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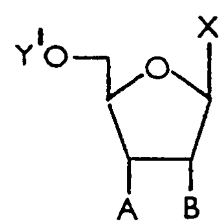
(54) Title: NUCLEOSIDE DERIVATIVES



(I)

(57) Abstract

Compounds of formula (I) wherein Y^1 is a hydrogen atom or an acyl or acyloxymethyl group; A and B are respectively a fluorine atom and a hydrogen atom or together represent a carbon-carbon bond; and X is a purine or pyrimidine base or an ester, amide or acyloxyalkyl derivative thereof. The compounds have antiviral activity.

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NUCLEOSIDE DERIVATIVES

This invention relates to antiviral compounds and more particularly to esters, ethers and amides of nucleoside derivatives which are active against human immunodeficiency virus (HIV), the retrovirus which causes the disease AIDS.

Since the recognition of AIDS as a new clinical entity in 1981 nearly five hundred thousand cases of the disease have probably been diagnosed, while the number of HIV infected persons is estimated to be between 5 million and 10 million.

AIDS is fatal, more than 50% of all diagnosed cases having ended in death. HIV and AIDS are today and will remain a worldwide health problem for many years to come.

Clinical symptoms are weight loss, chronic diarrhoea, persisting fever and opportunistic infections due to loss of T-cells, thus upsetting the overall balance of the immune system. The patient loses his/her ability to combat otherwise insignificant infections.

Several events in the replicative cycle can be considered as targets for chemotherapeutics; however, the most successful target so far has been reverse transcriptase, a vital enzyme in the life cycle of retroviruses.

Many substances interfering with replication have been tried, e.g. 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyadenosine, 3'-fluoroarabinosyladenine, 2',3'-dideoxycytidine, 2'-chloro-2,3'-dideoxyadenosine, 2',3'-dideoxyguanosine, 2',3'-dideoxyinosine, 2',3'-dideoxy-2',3'-didehydrothymidine, 3'-azido-2',3'-dideoxyuridine, 3'-azido-2',3'-dideoxy-5-ethyl-uridine, 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-ethyluracil, 2,6-diamino-9-(3'-azido-2',3'-dideoxy-β-D-erythropentofuranosyl) purine, suramin, Evans Blue,

fuchsin acid, 5-chloro-3'-fluoro-2',3'-dideoxy-uridine, hypericin, I-aurothioglucose, carbovir, dextran sulfate, interferon α, monoclonal antibodies against the HIV envelope, peptide T, phosphonoformate (foscarnet), phosphorothioate oligodeoxynucleotides, protease inhibitors, ribavirin and soluble CD4 receptor.

European Patent Application No. 0196185A, for instance, describes pharmaceutical compositions containing AZT, a known compound which has shown great promise in the treatment of AIDS and AIDS- related complex. It is believed that AZT works by inhibiting reverse transcriptase.

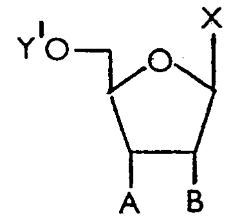
Further work has been done on alternative reverse transcriptase inhibitors which might avoid the limitations and drawbacks of AZT, for instance bone marrow suppression or the need for frequent administration of relatively large quantities, and among those suggested have been the 2',3'-dideoxy-3'-fluoronucleosides and 2',3'-dideoxy-2',3'-didehydro-nucleosides. Each type of compound has its advantages. For example, dideoxydidehydrothymidine has been found to be significantly less toxic than AZT in granulocyte macrophage progenitor cells (P. Herdewijn et al. in Pharmacochemistry Library 14, p.144 (1990)) although the compounds are equitoxic to other cell types, while 3'-fluoro-2',3'-dideoxy compounds are significantly more lipophilic than the corresponding 2',3'-dideoxy compouds.

The synthesis of some of these compounds has been described - see Biochem. Pharmacol. 37, 2847 (1988); J. Med. Chem. 31, 2040 (1988); J. Med. Chem. 32, 1743 (1988); and J. Med. Chem. 30, 2131 (1987); Biochem. Biophys. Res. Commun. 142, 128(1987); J. Org. Chem. 54, 4780 (1989); and J. Med. Chem. 83, 1911 (1989).

We have now found that acylation or alkylation of oxygen atoms in the 5'-position or in the purine or pyrimidine ring and/or acylation or alkylation of

exocylic or endocyclic nitrogen atoms present in the purine or pyrimidine ring can give significant advantages in terms of uptake, overall activity and site of action. Our PCT Application WO88/07532 describes certain esters and amides of this type carrying acyl groups at the 5' position or on exocyclic nitrogens; the present invention extends this principle to a wider range of related compounds.

Thus according to one feature of the invention we provide compounds of formula (I)



(I)

(wherein A is a fluorine atom and B is a hydrogen atom or A and B together represents a carbon-carbon bond

Y^1 is a hydrogen atom or a physiologically acceptable group of the formula

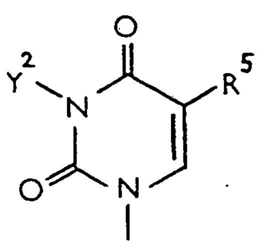
$R^1(O)_nCO(OCR^2R^3)_m$-

where n is 0 or 1, m is 0 or 1 and

R^1 is an optionally substituted alkyl or aryl group or an N-(C_{1-7} alkyl)-1,4-dihydropyridin- 3-yl group or, where n is 0, a hydrogen atom;

R^2 and R^3 are independently hydrogen atoms or lower alkyl groups; and

X is a group selected from



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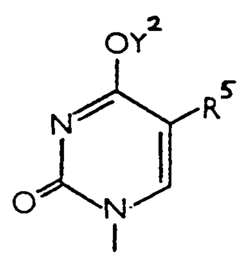

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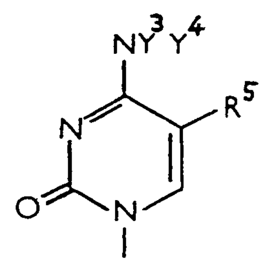

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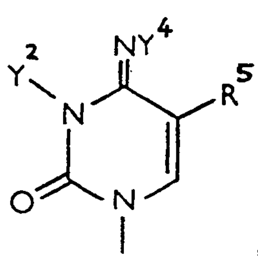

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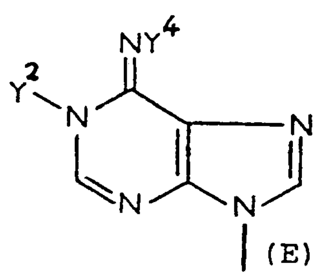

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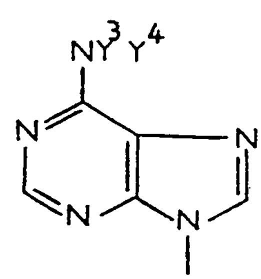

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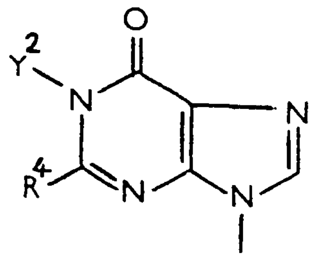

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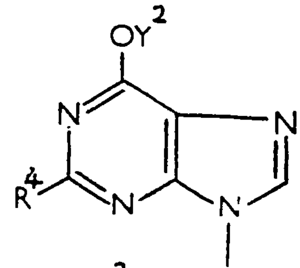

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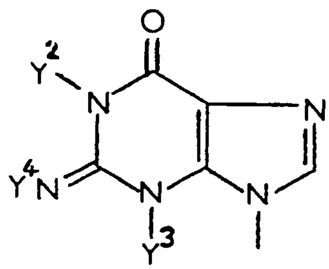
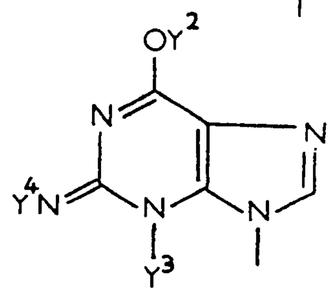


(I)



(J)

(where the groups Y^2, Y^3 and Y^4 are as defined for Y^1 and may be the same as or different from Y^1 or each other, R^4 is a hydrogen atom or a group $-NY^3Y^4$, where Y^3 and Y^4 have the above meanings and R^5 is a hydrogen or halogen atom or a lower alkyl or trifluoromethyl group, with the proviso that at least one of the groups Y^1, Y^2, Y^3 and Y^4 is other than hydrogen, and that when all of those groups Y^2, Y^3 and Y^4 which are present are hydrogen, then Y^1 is a group $R^1(O)_nCO(OCR^2R^3)_m$ in which n and/or m is 1) and/or salts thereof.

It will be appreciated that some of the groups X, for example those in which Y^2 is a hydrogen atom, are tautomers of other of the groups X and exist in equilibrium with them

According to a further feature of the invention we provide for the use of compounds of formula (I) as hereinbefore defined, and/or salts thereof, in the manufacture of a composition for the treatment or prophylaxis of retrovirus infections, in particular neurotropic viruses and especially HIV infections. Such compositions also form part of the invention.

The group R^1 is preferably an alkyl group

containing 1-20 carbon atoms which may be straight or branched, or an aryl group which may contain 6 to 20 carbon atoms and may be mono- or poly-cyclic. Substituents which may be present on the alkyl groups R^1 include aryl groups preferably having 6-10 carbon atoms (as in aralkyl groupings), alkoxy, hydroxy, acyloxy, amino, acylamino and carboxy groups. The acyl groups in the acyloxy and acylamino groups may be lower alkanoyl groups, e.g. C_{1-6} alkanoyl groups. Aryl groups include 5- or 6-membered heterocyclic aryl groups having one or more heteroatoms selected from O, N and S, such as furyl, imidazolyl, pyrrolyl, pyridinyl and thienyl groups. Substituents which may be present on aryl groups include alkyl groups, e.g. having 1-6 carbon atoms, hydroxy and carboxy groups. Examples of such groups include methyl, ethyl, propyl, t-butyl, pentyl, stearyl, palmityl, carboxyethyl and benzyl groups.

The lower alkyl groups R^2, R^3 and R^5 preferably contain 1-6 carbon atoms. However, R^2 preferably represents a hydrogen atom. R^3 is preferably a hydrogen atom or more preferably a methyl group. Where R^5 is a halogen atom it may be a fluorine, chlorine, bromine or iodine atom. However, R^5 is preferably a hydrogen or chlorine atom or a methyl group.

Where R^1 in any of the groups Y^1, Y^2, Y^3 or Y^4 is an N-alkyl-1,4-dihydropyridin-3-yl group the alkyl group is preferably methyl.

It will be noted that the compounds of the invention may carry more than one of the groups Y^1, Y^2, Y^3 and Y^4. In the compounds of formula (I) D,E, I and J, it is preferred that m in the group Y^4 is O (zero).

Groups Y^2 are preferably of the formula $R^1.CO-$, $R^1CO.O.CR^2R^3$ or $R^1.O.CO.O.CR^2R^3-$.

The salts of the compounds of formula (I) may be acid addition salts with organic or inorganic acids, for instance hydrochloric or phosphoric acid or methanesulphonic acid, ethane disulphonic acid, 2-naphthylsulphonic acid, pivalic acid and pamoic acid.

Antiviral counter-ions such as phosphonoformate or suramin may also be used. Organic or inorganic base salts may be formed with acidic groups present in the molecule; suitable counter-ions include alkali metal ions such as sodium and potassium ions, divalent ions such as calcium and zinc ions and organic ions such as tetraalkylammonium and choline or ions derived from meglumine or ethylenediamine. Salts according to the invention may be formed by reaction of the compound of formula (I) with an appropriate acid or base.

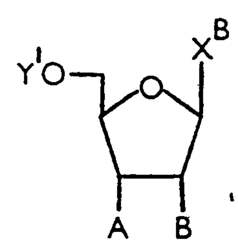
The compositions according to the invention may be used in the treatment and/or prophylaxis of retrovirus infections, in particular HIV infections, and such a method forms a further feature of the invention. They may be formulated in conventional manner by admixture of one or more compounds of formula (I) as defined above with excipients and/or carriers.

While the compounds of formula (I) may themselves be inhibitors of reverse transcriptase when the 5'-hydroxy group is free it is also possible that they are converted <u>in vivo</u> to the 5'-hydroxy-2',3'-dideoxy-3'-fluoronucleosides or 5'-hydroxy-2',3'-dideoxy-2',3'-didehydro nucleosides. Nevertheless the substitution at the respective O- and N- atoms gives surprising advantages in terms of uptake and sustained activity. The compounds of formula (I) are more lipophilic than the parent compounds and this permits rapid and efficient absorption from the gastro-intestinal tract; the absorption rate may be optimised by careful choice of the substituent group to give the desired balance of lipophilicity and hydrophilicity. The lipophilic nature of the compounds of formula (I) also gives the molecules the ability to penetrate the cell membranes more easily and leads to higher intracellular concentrations, giving an improved dose/effect ratio. The steady hydrolysis of the compounds ensures a sustained concentration of the active compound in the cell and thereby permits longer

intervals between doses, overcoming a significant drawback of the prior art compounds. Finally, the compounds according to the invention can penetrate the blood-brain barrier and thus permit treatment of the neurological disorders which have been observed to be related to the presence of neurotropic viruses, e.g. retroviruses such as HIV, and lentiviruses (Yarchoan et al, The Lancet, January 17, 1987, page 132). This is a significant advantage compared to the corresponding unsubstituted compounds or other antiviral compounds and is not referred to anywhere in the prior art. Attempts have been made to treat these neurological disorders with AZT but with limited success.

The invention thus further provides a method of treatment of neurological disorders caused by neurotropic viruses wherein an effective dose of a compound of formula (I) or a salt thereof is administered to a patient suffering from such a disorder.

Compounds of formula (I) may be prepared in any convenient way, for example, by reaction of a compound of formula (II)



(II)

[wherein A, B and Y^1 are as hereinbefore defined and X^B is as hereinbefore defined for X except that any of the groups Y^1, Y^2, Y^3 and Y^4 may each additionally represent a protecting group, with the proviso that at least one of Y^1, Y^2, Y^3 and Y^4 is a hydrogen atom] with a reagent serving to introduce a group $R^1(O)_nCO.(OCR^2R^3)_m$ as defined above followed where required by removal of any protecting groups and/or unwanted substituents so introduced.

It should be noted that where, in the starting material, more than one of Y^1, Y^2, Y^3 and Y^4 is hydrogen, multiple reactions may occur.

Where it is desired to ensure that acylation or alkylation is effected while one or more groups Y^1, Y^2, Y^3 and Y^4 remain as hydrogen atoms, it may be desirable to protect the latter first, to form a compound of formula (I) in which one or more of Y^1, Y^2, Y^3 and Y^4 are protecting groups, these being removed after introduction of the desired acyl or ether group. Such protecting groups may, in fact, be conventional N- or O-protecting groups including groups R^1OCO- which may be selectively removed in the presence of the group(s) intended to remain. Thus, for example, an N-benzyloxycarbonyl may be used to protect an exocylic amino group and if the group which is intended to remain is not one which is removable by reduction, for example a straight chain alkoxycarbonyl group, the N-benzyloxycarbonyl group can readily be removed selectively using hydrogen and a noble metal catalyst such as palladium. Trisubstituted silyl groups may also be used as protecting groups, especially for the 5'-oxygen atom, and include trialkylsilyl e.g. trimethylsilyl, dimethyl- t-butylsilyl, and thexyldimethyl silyl groups.

In general, where more than one of Y^1, Y^2, Y^3 and Y^4 are hydrogen, and a mixture of compounds is produced, the individual components may readily be separated, for example by chromatography.

Where 5'-O-monoalkylation is to be effected (i.e. introduction of a group Y^1 in which m is 1) it is especially effective to form a dianion of the nucleoside (e.g. by reacting with sodium hydride) and to react this with one equivalent of the alkylating agent. It is of course, still possible to use protected forms of the nucleoside, for example by acylation of a nucleophilic nitrogen atom before salt formation with sodium hydride.

Suitable acylating agents for use in the reaction have the formula Ac-L where L is a leaving group. When the acyl group Ac- is derived from a carboxylic acid, i.e. is of formula R^1-CO-, then suitable acylating agents include the acid halides and acid anhydrides advantageously in the presence of a base; when the acyl group is derived from a carbonic acid, i.e. is of formula R^1.O.CO-, then acylating agents include the haloformate esters and reactive carbonic acid diesters. In such reagents, the halogen may, for example, be chlorine or bromine. The base for use in the reaction with the acid halide or anhydride may, for example, be a heterocyclic base such as pyridine or 4-dimethylaminopyridine. The latter increases the speed of the reaction and may be used advantageously with pyridine. The reaction will normally be carried out in the presence of an inert solvent e.g. a substituted amide solvent such as dimethylformamide, dimethylacetamide or a halogenated hydrocarbon such as dichloromethane.

In general, we have found that using acid anhydrides as acylating agents to introduce a group R^1CO, O-acylation at the 5'- position takes place more readily than N-acylation, whereas using acid halides, N-acylation or even N-diacylation predominates. However, N-acyl groups R^1CO- may be removed selectively, for example by reaction with a phenol such as p-methyl-phenol. Where multiple substitution is to be effected, a stronger base such as sodium hydride may be advantageous.

It has also been found that an α-acetoxyisobutyryl group in the 5'-position may be selectively removed by sodium hydride/ammonia in the presence of a group R^1.O.CO.NH- on the base. This may conveniently be used in the preparation of N-acyl compounds by blocking the 5'-position, N-acylation and deblocking of the 5'-position.

Suitable acyloxyalkylating agents for use in the invention will in general be of the formula $R^1CO.O.CR^2R^3L$ or $R^1O.CO.O.CR^2R^3L$, where L is a leaving group. Thus, the group L may for example, be a halogen atom such as a chlorine or bromine atom or a hydrocarbon-sulphonyloxy group such as a tosyloxy or mesyloxy group.

The alkylation reaction will normally be effected in the presence of a base, conveniently an inorganic carbonate such as potassium carbonate or an alkali metal hydride such as sodium hydride. Bases as used for acylation may also be useful.

The starting compounds of formula (II) wherein Y^1, Y^2, Y^3 and Y^4 are all hydrogen atoms are well described in the literature (see for example the literature references cited in the introduction hereto). Starting compounds wherein one or more of Y^1, Y^2, Y^3 and Y^4 are other than hydrogen may be prepared by preliminary reactions as described above.

The pharmaceutical compositions according to the invention may be formulated conventionally by means well known in the art, and may be administered by any convenient route, for instance orally, rectally, vaginally, intraveneously or intramuscularly. Examples of suitable formulations include tablets and capsules, aqueous formulations for intravenous injection and oil-based formulations for intramuscular injection. Suitable dosages will lie in the range 0.1 to 100mg per kilogram of bodyweight per 24 hour period. The compositions according to the invention may also contain other active antivirals for instance acyclovir, phosphonoformate, suramin, Evans Blue, interferons or AZT.

The invention is illustrated by the following Examples.

Example 1

3'-Fluoro-3-pivaloyloxymethyl-3'-deoxythymidine

3'-Fluoro-3'-deoxythymidine (0.2 mmol) and imidazole (0.5 mmol) are dissolved in DMF (0.5 mmol). Thexyldimethylsilyl chloride (0.25 mmol) is added, and the reaction mixture is stirred at ambient temperature for 24 hours. The solvent is removed at reduced pressure, chloroform (15 ml) added to the residue, washed with water (5 ml x 2), and the dried ($MgSO_4$) solution evaporated. The residue is chromatographed on silica gel using ethyl acetate-hexane to furnish 3'-fluoro-5'- O-thexyldimethylsilyl-3'-deoxythymidine.

The product thus prepared (0.1 mmol) and potassium carbonate (0.12 mmol) are added to DMF (1 ml), the mixture stirred for 1.5 hours at ambient temperature, cooled to 0°C, chloromethyl pivalate (0.12 mmol) added, the mixture stirred at ambient temperature for 18 hours, the solvent evaporated at reduced pressure, and the residue chromatographed on silica gel using ethyl acetate-hexane to furnish 3'-fluoro-3-pivaloyloxymethyl-5'-O-thexyldimethylsilyl-3'-deoxythymidine.

The silyl group is removed by dissolution of the product thus obtained (1 mmol) in THF (1 ml) and adding 0.25 M solution of tetrabutylammonium fluoride in THF (1 ml). The mixture is stirred at ambient temperature for 30 minutes, the solvent evaporated, the residue dissolved in chloroform (10 ml), washed with water (2 ml), dried ($MgSO_4$), evaporated, and the residue purified by preparative chromatography on silica gel plates using diethyl ether. The title compound is extracted from the main band by chloroform-methanol.

Example 2

3-α-(Ethyloxycarbonyloxy)ethyl-5-chloro-3'-fluoro-5'-O-propionyl-2',3'-dideoxyuridine

5-Chloro-3'-fluoro-2',3'-dideoxyuridine (0.2 mmol) and 4-N,N-dimethylaminopyridine (0.25 mmol) are dissolved in pyridine (3 ml), the solution cooled to 0°C, propionic anhydride (0.3 mmol) added, the mixture stirred at ambient temperature for 24 hours, the solvent evaporated at reduced pressure, toluene added, the mixture reevaporated at reduced pressure, and the residue chromatographed on silica using chloroform and subsequently chloroform- methanol. The product obtained is 5-chloro-3'-fluoro-5'-O-propionyl-2',3'-dideoxyuridine.

5-chloro-3'-fluoro-5'-O-propionyl-2',3'-dideoxyuridine (0.2 mmol) and potassium carbonate (0.25 mmol) are suspended in DMF (2 ml), the mixture stirred at ambient temperature under nitrogen for 1.5 hours, cooled to 0°C, 1-chloroethyl ethyl carbonate (0.25 mmol) added, the mixture stirred at 0°C for 30 minutes, at ambient temperature for 2 hours, at 60°C for 24 hours, and the solvent evaporated at reduced pressure. The title compound is purified by chromatography of the residue on silica gel using ethyl acetate-hexane.

Example 3

3'-Fluoro-5'-pivaloyloxymethyl-2',3'-dideoxyinosine

A mixture of 3'-fluoro-2',3'-dideoxyinosine (0.1 mmol) and sodium hydride (0.2 mmol) in DMF (1.5 mmol) is stirred at 0°C for 1.5 hours, chloromethyl pivalate (0.11 mmol) added, the mixture stirred for 1 hour at ambient temperature, acetic acid (1 mmol) added, the

solvent evaporated at reduced pressure, and the residue chromatographed on silica gel. The product is eluted with chloroform- methanol.

Example 4

N^4-Benzyloxycarbonyl-3'-fluoro-2',3'-dideoxycytidine

3'-Fluoro-2',3'-dideoxycytidine (0.2 mmol) is dissolved in a mixture of pyridine (0.5 ml) and DMF (0.5 ml), the solution cooled to 0°C, benzyl chloroformate (0.5 mmol) and 4-N,N-dimethylamino- pyridine (0.2 mmol) added, the mixture stirred at ambient temperature for 12 hours, water (4 ml) added, the mixture evaporated at reduced pressure, and the residue chromatographed on silica gel. The title compound is eluted with chloroform:ethanol (99:1).

Example 5

N^4-Benzyloxycarbonyl-3'-fluoro-5'-O-pivaloyloxymethyl 2',3'-dideoxycytidine

A mixture of N^4-benzyloxycarbonyl-3'-fluoro-2',3'-dideoxycytidine (0.1 mmol) and sodium hydride (0.21 mmol) in DMF (2 ml) is stirred at ambient temperature for 1.5 hours, the mixture cooled to -50°C, chlormethyl pivalate (0.11 mmol) added, the mixture stirred at -50°C for 4 hours, saturated ammonium chloride solution (1 ml) added, the mixture evaporated at reduced pressure, and the residue chromatographed on silica. The product is eluted with chloroform-methanol.

Example 6

3'-Fluoro-5'-O-pivaloyloxymethyl-2',3'-dideoxycytidine

N^4-Benzyloxycarbonyl-3'-fluoro-5'-O-pivaloyloxymethyl-2',3'-dideoxycytidine (0.1 mmol) is added to a suspension of 5% palladium on charcoal (8 mg) in ethanol (4 ml). The hydrogenolysis is run at atmospheric pressure using a Brown apparatus where the hydrogen gas is generated in a controlled manner by the addition of 3 N HCl to a solution of sodium hydride in a separate compartment. The reaction is run at ambient temperature and is monitored by TLC in order to ensure that over-reduction in the heterocyclic ring does not occur. The reaction time is normally about 1 hour. The mixture is then filtered through a thin bed of Celite, the filtrate evaporated and the product purified by chromatography on silica gel using chloroform:ethanol (9:1).

Example 7

3'-Fluoro-4-O-(1-methyl-1,4-dihydro-3-pyridinylcarbonyl) - 3'-deoxythymidine

3'-Fluoro-3'-deoxythymidine(0.2 mmol) and imidazole (0.5 mmol) are dissolved in DMF (0.5 mmol). Thexyldimethylsilyl chloride (0.25 mmol) is added, and the reaction mixture is stirred at ambient temperature for 24 hours. The solvent is removed at reduced pressure, chloroform (15 ml) added to the residue, washed with water (5 ml x 2), and the dried ($MgSO_4$) solution evaporated. The residue is chromatographed on silica gel using ethyl acetate-hexane to furnish 3'-Fluoro-5'- O-thexyldimethylsilyl-3'-deoxythymidine.

The product thus prepared (0.1 mmol) is added to THF (4 ml) containing N,N'-dicyclohexylcarbodi- imide (0.11 mmol) and hydroxybenzotriazole (1 mg) followed by 1-methyl-1,4-dihydronicotinic acid (0.11 mmol). The mixture is stirred at ambient temperature for 24 hours, filtered, the solid washed with ethyl acetate, the

combined filtrates evaporated to dryness, and the residue chromatographed on silica gel using ethyl acetate-hexane to furnish 3'-Fluoro-4-O-(1-methyl-1,4-dihydro-3-pyridinylcarbonyl)- 5'-O-thexyldimethylsilyl-3'-deoxythymidine.

The silyl group is removed by dissolution of the product (1 mmol) in THF (1 ml) and adding 0.25 M solution of tetrabutylammonium fluoride in THF (1 ml). The mixture is stirred at ambient temperature for 20 minutes, the solvent evaporated, the residue dissolved in chloroform (10 ml), washed with water (2 ml), dried ($MgSO_4$), evaporated, and the residue purified by preparative chromatography on silica gel using chloroform-methanol.

Example 8

3'-Fluoro-4-O-(1-methyl-1,4-dihydro-3-pyridinylcarbonyl) - 5'-O-propionyl-3'-deoxythymidine

3'-Fluoro-4-O-(1-methyl-1,4-dihydro-3-pyridinylcarbonyl) - 3'-deoxythymidine (0.1 mmol) and 4-N,N-dimethylamino-pyridine (0.13 mmol) are dissolved in pyridine (3 ml), the solution cooled to 0°C, propionic anhydride (0.12 mmol) added, the mixture stirred at ambient temperature for 12 hours, the solvent evaporated at reduced pressure, toluene added, the mixture reevaporated at reduced pressure, and the residue chromatographed on silica gel using ethyl acetate- hexane to yield the title compound.

Example 9

1-(5-O-Pivaloyloxymethyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)thymine

A mixture of 1-(2,3-dideoxy-ß-D-glycero-pent-

2-enofuranosyl)thymine and sodium hydride (0.2 mmol) in DMF (1.5 ml) is stirred at 0°C for 1.5 hours, chloromethyl pivalate (0.11 mmol) added, the mixture stirred for 1 hour at ambient temperature, acetic acid (1 mmol) added, the solvent evaporated at reduced pressure, and the residue chromatographed on silica gel. The product is eluted with chloroform-methanol.

Example 10

3-α-(Ethoxycarbonyloxy)ethyl-1-(5-O-propionyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)uracil

1-(2,3-Dideoxy-ß-D-glycero-pent-2-enofuranosyl)uracil (0.2 mmol) and 4-N,N-dimethylaminopyridine (0.25 mmol) are dissolved in pyridine (3 ml), the solution cooled to 0°C, propionic anhydride (0.3 mmol) added, the mixture stirred at ambient temperature for 24 hours, the solvent evaporated at reduced pressure, toluene added, the mixture reevaporated at reduced pressure, and the residue chromatographed on silica using chloroform and subsequently chloroform- methanol. The product thus obtained is 1-(5-O-propionyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl) uracil.

1-(5-O-propionyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)uracil (0.2 mmol) and potassium carbonate (0.25 mmol) are suspended in DMF (2 ml), the mixture stirred at ambient temprature under nitrogen for 1.5 hours, cooled to 0°C, 1-chloroethyl ethyl carbonate (0.25 mmol) added, the mixture stirred at 0°C for 30 minutes, at ambient temperature for 2 hours, at 60°C for 24 hours, and the solvent evaporated at reduced pressure. The residual product is purified by chromatography on silica gel using ethyl acetate-hexane.

Example 11

1-(5-O-Pivaloyloxymethyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine

t-Butylmagnesium chloride (0.1 mmol) in dry THF (2 ml) is added to a stirred mixture of 1-(2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine (0.1 mmol) in dry THF (3 ml) at 0°C, the mixture stirred at this temperature for 2 hours, dry pyridine (2 ml) added, the stirring continued for 1 hour, chloromethyl pivalate (0.11 mmol) added, the mixture stirred for 1 hour at 0°C and for 1 hour at ambient temperature, water (2 ml) added, the solvent evaporated at reduced pressure, and the residue chromatographed on silica gel. The product is eluted with chloroform- ethanol.

Example 12

N^4-Ethyloxycarbonyl-1-(2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine

1-(2,3-Dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine (0.1 mmol) is dissolved in a mixture of pyridine (0.5 ml) and DMF (0.5 ml), the solution cooled to 0°C, ethyl chloroformate (0.3 mmol) and 4-N,N-dimethylaminopyridine (0.15 mmol) added, the mixture stirred at ambient temperature for 12 hours, water (4 ml) added, the mixture evaporated at reduced pressure, and the residue chromatographed on silica gel. The title compound is eluted with chloroform:ethanol (99:1).

Example 13

N^4-Ethyloxycarbonyl-1-(5-O-pivaloyloxymethyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine

A mixture of N^4-ethyloxycarbonyl-1-(2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)cytosine (0.1 mmol) and sodium hydride (0.21 mmol) in DMF (2 ml) is stirred at ambient temperature for 1.5 hours, the mixture cooled to -50°C, chloromethyl pivalate (0.11 mmol) added, the mixture stirred at -50°C for 4 hours, saturated ammonium chloride solution (1 ml) added, the mixture evaporated at reduced pressure, and the residue chromatographed on silica. The product is eluted with chloroform-methanol.

Example 14

4-O-(1-Methyl-1,4-dihydro-3-pyridinylcarbonyl)-1-(2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)thymine

1-(2,3-Dideoxy-ß-D-glycero-pent-2-enofuranosyl)- thymine (0.2 mmol) and imidazole (0.5 mmol) are dissolved in DMF (0.5 mmol). Thexyldimethylsilyl chloride (0.25 mmol) is added, and the reaction mixture is stirred at ambient temperature for 24 hours. The solvent is removed at reduced pressure, chloroform (15 ml) added to the residue, washed with water (5 ml x 2), and the dried ($MgSO_4$) solution evaporated. The residue is chromatographed on silica gel using ethyl acetate-hexane to furnish 1-(5-O-thexyldimethylsilyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)thymine.

The product thus prepared (0.1 mmol) is added to THF (4 ml) containing N,N'-dicyclohexylcarbodi- imide (0.11 mmol) and hydroxybenzotriazole (1 mg) followed by 1-methyl-1,4-dihydronicotinic acid (0.11 mmol). The mixture is stirred at ambient temperature for 24 hours, filtered, the solid washed with ethyl acetate, the combined filtrates evaporated to dryness, and the residue chromatographed on silica gel using ethyl

acetate- hexane to furnish 4-O-(1-methyl-1,4-dihydro-3-pyridinylcarbonyl)-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)- thymine.

The silyl group is removed by dissolution of the product (1 mmol) in THF (1 ml) and adding 0.25 M solution of tetrabutylammonium fluoride in THF (1 ml). The mixture is stirred at ambient temperature for 15 minutes, the solvent evaporated, the residue dissolved in chloroform (10 ml), washed with water (2 ml), dried ($MgSO_4$), evaporated, and the residue purified by preparative chromatography on silica gel using chloroform-methanol.

Example 15

4-O-(1-Methyl-1,4-dihydro-3-pyridinylcarbonyl)-1-(5-O-propionyl-2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)thymine

4-O-(1-Methyl-1,4-dihydro-3-pyridinylcarbonyl)-1-(2,3-dideoxy-ß-D-glycero-pent-2-enofuranosyl)- thymine (0.1 mmol) and 4-N,N-dimethylaminopyridine (0.13 mmol) are dissolved in pyridine (3 ml), the solution cooled to 0°C, propionic anhydride (0.12 mmol) added, the mixture stirred at ambient temperature for 12 hours, the solvent evaporated at reduced pressure, toluene added, the mixture reevaporated at reduced pressure, and the residue chromatographed on silica gel using ethyl acetate- hexane.

Example 16

3-Pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine

a. 3-Pivaloyloxymethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine. Potassium carbonate (0.196 g, 0.890 mmol) was added to a solution of 1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyll)thymine (0.196 g, 0.536 mmol) in dry DMF (5 ml) under nitrogen, the mixture stirred at ambient temperature for 1 hour, cooled to 0°C, chloromethyl pivalate (0.100 ml, 0.698 mmol) added and the mixture stirred at ambient temperature for 17 hours before the solvent was removed under reduced pressure. The residue was extracted with chloroform, the mixture filtered, the filtrate evaporated and the product purified by chromatography on the "chromatotron" (Harrison Research) using ethyl acetate: hexane (1:2); yield 0.213 g (83%) of an almost colourless oily material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (Me_2Si), 0.84 (4 x Me-thex), 1.14 (Me_3C), 1.54 (CH-thex), 1.88 (5-Me), 3.78 (5'-CH_2), 4.82 (H-4'), 5.82 (H-2'), 5.92 (OCH_2N), 6.26 (H-3'), 6.95 (H-1'), 7.29 (H-6)

^{13}C NMR (50 MHz, $CDCl_3$): δ -3.25/-3.18 (Me_2Si), 18.56/18.66/20.31/20.62/23.33/27.23 (7 x Me), 25.69 (C-thex), 34.20 (CH-thex), 39.05 ($Me_3\underline{C}$), 64.91 and 65.48 (5'-CH_2 and OCH_2N), 87.47 (C-4'), 90.95 (C-1'), 110.48 (C-5), 126.70 (C-2'), 135.33 (C-3'), 135.39 (C-6), 151.40 (C-2), 163.22 (C-4), 178.19 (CO-ester).

b. 3-Pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine. A solution of anhydrous tetrabutylammonium fluoride in dry THF (0.25M; 2.5 ml)

was added dropwise with stirring to a solution of 3-pivaloyloxymethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyll)thymine (0.213 g, 0.444 mmol) under nitrogen at 0°C. The solution was stirred at ambient temperature for 30 min before saturated aqueous ammonium chloride solution (8 ml) was added, the mixture stirred for 15 min and evaporated to dryness at reduced pressure, the residue extracted with chloroform, the mixture filtered, the filtrate evaporated and the residual product purified by chromatography on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.122 g (81 %) of a white crystalline solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (Me_3C), 1.82 (5-Me), 3.81 (5'-CH_2), 4.86 (H-4'), 5.80 (H-2'), 5.88 (CH_2), 6.28 (H-3'), 6.96 (H-1'), 7.58 (H-6).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.20 (5-Me), 27.71 ($\underline{Me_3}C$), 39.5 ($Me_3\underline{C}$), 63.64 (CH_2), 65.50 (C-5'), 87.57 (C-4'), 90.96 (C-1'), 110.42 (C-5), 127.00 (C-2'), 135.05 and 136.39 (C-6' and C-3'), 151.52 (C-2), 163.37 (C-4), 178.42 (CO-ester).

Example 17

1-(5-O-Ethyloxycarbonyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)3-pivaloyloxymethylthymine

a. 1-(5-O-Ethyloxycarbonyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine. Diethyl pyrocarbonate (0.250 ml, 1.728 mmol) was added with stirring to a solution of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.139 g, 0.621 mmol) and DMAP (0.114 g, 0.934 mmol) in pyridine (10 ml) under nitrogen at 0°C. The mixture was stirred at ambient temperature for 2.5 hours before the pyridine was removed at reduced pressure. Any residual pyridine was removed by the

addition of toluene (20 ml) followed by re-evaporation. The residual material was dissolved in chloroform:ethanol (4:1), the solution filtered through silica gel (thickness 3 cm), the filtrate evaporated and the product purified by chromatography on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.167 g (90%) of a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 and 4.2 (OEt), 1.88 (5-Me), 4.1-4.4 (5'-CH_2), 5.00 (H-4'), 5.84 (H-2'), 6.27 (H-3'), 7.03 (H-1'), 9.11 (NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.41 and 14.42 (2 x Me), 64.86 (5'-CH_2), 67.60 (Me$\underline{CH_2}$O), 84.35 (C-4'), 89.74 (C-1'), 111.68 (C-5'), 128.13 (C-2'), 133.45 (C-3'), 136.78 (C-6), 151.54 (C-2), 155.40 (C-4), 164.54 (CO-ester).

b. <u>1-(5-O-Ethyloxycarbonyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)3-pivaloyloxymethylthymine</u>. Potassium carbonate (0.077 g, 0.557 mmol) was added to a solution of 1-(5-O-ethyloxycarbonyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.136g, 0.459 mmol) in DMF (13 ml) under nitrogen, the mixture stirred vigorously at ambient temperature for 45 min, cooled to 0°C and chloromethyl pivalate (0.080 ml, 0.558 mmol) added. The mixture was stirred at ambient temperature for 21 hours before the solvent was removed at reduced pressure. The residue was extracted with chloroform, the mixture filtered, the filtrate evaporated and the product purified by chromatography on the "chromatotron" using hexane:ethyl acetate (1:1); yield 0.186 g (96%) of a crystalline solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (Me_3C) 1.20 and 4.2 (OEt), 1.87 (5-Me), 4.1-4.4 (5'-CH_2), 4.98 (H-4'), 5.85 (OCH_2N and H-2'), 6.25 (H-3'), 7.02 (H-1'), 7.39 (H-6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.93 and 14.38 (5-Me and <u>Me</u>CH_2), 27.18 (<u>Me_3</u>C), 39.02 (Me_3<u>C</u>), 64.78 (Me<u>CH_2</u>O), 65.49 (C-5'), 67.52 (OCH_2N), 84.37 (C-4), 90.47 (C-1'), 110.81 (C-5), 127.97 (C-2'), 133.61 (C-3'), 135.82 (C-6), 151.49 (C-2), 155.27 (CO-piv. ester),162.40 (C-4), 178.20 (CO-carbonate).

<u>Example 18</u>

<u>3-α-(Ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine</u>

a. <u>1-(5-O-Thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine</u>. Thexyldimethylsilyl chloride (1.00 ml, 5.10 mmol) was added to a solution of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (1.130 g, 5.05 mmol) and imidazole (0.948 g, 13.94 mmol) in dry DMF (15 ml) under nitrogen and the mixture stirred at ambient temperature for 2 hours before the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel using chloroform:ethanol (8:1); yield 1.842 g (98 %) of a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (Me_2Si), 0.83 (4 x Me-thex), 1.60 (Me_2<u>CH</u>), 1.89 (5-Me), 3.79 (5'-CH_2), 4.84 H-4'), 5.81 (H-2'), 6.28 (H-3'), 6.95 (H-1'), 7.27 (H-6), 8.54 (N-H).

^{13}C NMR (50 MHz,$CDCl_3$): δ -7.6 (Me_2Si), 16.0/16.2 (4 x Me-thex) 21.29 (Me_2<u>C</u>Si), 29.81 (Me_2<u>CH</u>-thex), 60.53 (C-5') 82.97 (C-4'), 85.71 (C-1'), 106.90 (C-5), 122.31 (C-2'), 130.86 and 131.94 (C-6 and C-3'), 146.97 (C-2), 159.8 (C-4).

b. <u>3-α-(Ethyloxycarbonyloxy)ethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-</u>

enofuranosyl)thymine. Anhydrous potassium carbonate (0.112 g, 0.883 mmol) was added to a solution of 1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.200 g, 0.546 mmol) in DMF (7 ml). The suspension was stirred vigorously under nitrogen at ambient temperature for 1 hour, cooled to 0°C and chloroethyl ethyl carbonate (0.100 ml, 0.748 mmol) added, the mixture stirred at 40°C overnight, additional chloroethyl ethyl carbonate (0.05 ml, 0.374 mmol) added and the mixture stirred at 40°C for another 3 hours. The solvent was then removed at reduced pressure, the residue extracted into hexane: ethyl acetate (2:1) and chromatographed on the "chromatotron"; yield 0.143 g (54 %) of a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (Me_2Si), 0.84 (4 x Me-thex, MeCH), 1.22 and 4.14 (OEt), 1.85 (5-Me, CH), 4.80 (H-4'), 5.80 (H-2'), 6.39 (H-3'), 6.95 (H-1'), 7.23 (H-6 and MeCH).

^{13}C NMR (50 MHz, $CDCl_3$): δ -1.36 (Me_2Si), 14.26 (5-Me), 18.64/18.73/20.28 (6 x Me) 20.28 (Me_2CSi), 25.05 (Me_2CH) 34.31 (CH_2O), 64.90 (C-5'), 77.79 (MeCHO), 87.34 (C-4'), 90.64/90.76 (C-1'), 105.90 (C-5), 126.82/126.91 (C-2'), 135.16 and 135.08 (C-6 and C-3'), 154.20 (C-2), 162.70 (CO-ester).

c. 3-α-(Ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine. A solution of anhydrous tetrabutylammonium fluoride in dry DMF (0.25M; 1.00 ml, 0.250 mmol) was added dropwise with stirring to a solution of 3-α-(ethyloxycarbonyloxy)ethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.96 g, 0.199 mmol) in dry THF (5 ml) under nitrogen at 0°C and the mixture stirred at ambient temperature for 30 min. Saturated aqueous ammonium chloride solution was then added, the mixture stirred for 30 min, evaporated at reduced pressure, the residue extracted with chloroform, the mixture filtered, the filtrate evaporated and the residual product purified on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.055 g (80%) of a colourless oily material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (5-Me), 1.22 and 4.18 (OEt), 1.83 (<u>Me</u>CH), 3.83 (5'-CH_2), 4.88 (H-4'), 5.84 (H-2'), 6.30 (H-3'), 7.02 (H-1'), 7.25 (Me<u>CH</u>), 7.42 (H-6).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.28 and 14.30 (5-Me and <u>Me</u>CH_2), 18.13 (<u>Me</u>CH), 64.00 and 63.79 (5'-CH_2 and Me<u>CH_2</u>O), 77.88 (Me<u>CH</u>), 87.39 (C-4'), 90.75 (C-1'), 110.78 (C-5), 127.19 (C-2'), 135.65 and 134.85 (C-6 and C-3'), 150.20 (C-2), 153.20 (C-4), 163.34 (CO-ester).

Example 19

3-α-(Ethyloxycarbonyloxy)ethyl-1-(5-O-ethyloxycarbonyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-α-(ethyloxycarbonyloxy)ethylthymine

Diethyl pyrocarbonate (0.200 ml, 2.76 mmol) was added to a stirred solution of 3-α-(ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.027 g, 0.079 mmol) and DMAP (0.014 g, 0.115 mmol) in pyridine (5 ml) under nitrogen at 0°C and the mixture

stirred at ambient temperature for 17 hours. The pyridine was then distilled off at reduced pressure. Any residual pyridine was removed by addition of toluene (20 ml) and re-evaporation, the residue dissolved in chloroform:ethanol (4:1), filtered through silica gel (3 cm thick layer), the filtrate evaporated and the product purified by chromatography using the "chromatotron" and chloroform:diethyl ether (1:1); yield 0.030 g (92%) of an oily material

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 and 4.1-4.4 (2 x OEt), 1.86 (5-Me and <u>Me</u>CH), 4.1-4.4 (5'-CH_2), 5.00 (H-4'), 5.86 (H-2'), 6.24 (H-3'), 7.1-7.4 (H-6, Me<u>CH</u> and H-1').

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.03/14.31/14.42 (3 x Me), 18.08 (<u>Me</u>CH), 64.84 and 64.66 (2 x Me<u>CH_2</u>O), 67.60 (C-5'), 76.85 (Me<u>CH</u>), 84.32 (C-4'), 90.25 (C-1'), 111.00 (C-5), 128.21 (C-2'), 135.48 and 133.40 (C-6 and C-3'), 155.38 (C-2), 163.25 (CO-ester).

<u>Example 20</u>

<u>3-α-(Ethyloxycarbonyloxy)ethyl-1-(5-O-pivaloyloxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-α-(ethyloxycarbonyloxy)ethylthymine</u>. Sodium hydride (0.005g, 0.167 mmol) was added to a stirred solution of 3-α-(ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.028 g, 0.082 mmol) in DMF (5 ml) at 0°C, the mixture stirred for 1 hour before chloromethyl pivalate (0.015 ml, 0.105 mmol) was added and the mixture stirred at ambient temperature for 24 hours. Saturated aqueous ammonium chloride solution (10 ml) was then added, the mixture evaporated to dryness at reduced pressure, the residue extracted with chloroform, the filtrate evaporated and the product purified by chromatography on the "chromatotron" using chloroform:diethyl ether (1:1); colourless oily material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (Me_3C), 1.31 (Me), 1.8-1.9 (2 x Me), 4.1-4.4 (5'-CH_2 and O$\underline{CH_2}$Me), 5.02 (H-4'), 5.8-5.9 (OCH_2O and H-2'), 6.27 (H-3'), 7.1-7.4 (H-6, Me$\underline{CH}$O and H-1').

Example 21

3-Pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil

a. 1-(5-O-Thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil. Thexyldimethylsilyl chloride (100 mg, 0.56 mmol) was added to a solution of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (97 mg, 0.46 mmol) and imidazole (80 mg, 1.18 mmol) in dry DMF (1 ml) under nitrogen and the mixture stirred at ambient temperature for 19 hours before the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel using ethyl acetate: hexane (7:3); yield 100 mg (61 %) of a white solid.

^{1}H NMR (200 MHz, DMSO-$\underline{d}_6$) δ:0.01 (s, Me_2Si), 0.74 (s, $\underline{Me_2}$C-thex), 0.77 (d, $\underline{Me_2}$CH-thex, $\underline{J}$ 7 Hz), 1.5 (m, C$\underline{H}$$Me_2$-thex, $\underline{J}$ 7 Hz), 3.70 (5'-CH_2), 4.76 (H-4'), 5.54 (d, H-5), 5.9 (m,H-2'), 6.3 (m,H-3'), 6.73 (m,H-1'), 7.63 (d, H-6).

^{13}C NMR (50 MHz,DMSO-$\underline{d}_6$) δ:$SiCH_3$ not observed, 18.2,18.4, 20.0,20.3 (4 X thexyl CH_3), 24.9(Si$\underline{C}Me_2$), 33.6(CH$\underline{Me_2}$), 64.4 (C5'), 87.1 (C4'), 89.3 (Cl'), 101.9 (C5), 126.5(C2'), 134.9 (C3'), 141.11 (C6), 151.03 (C2), 163.5 (C4)

b. 3-Pivaloyloxymethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil. Potassium carbonate (1.037 g, 7.4 mmol) was added to a solution of 1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-

glycero-pent-2-enofuranosyl)uracil (2.191 g, 6.22 mmol) in dry DMF (20 ml) under nitrogen, the mixture stirred at 70°C for 1 hour, cooled to 0°C, chloromethyl pivalate (1.52 g, 10 mmol) added and the mixture stirred at 70°C for 3 hours. Water was added and the mixture freeze-dried and the residue subjected to flash chromatography on silica using ethyl acetate:hexane (5:7); yield 2.120 g (76 %) of a colourless oily material.

^{1}H NMR (200 MHz,DMSO-$\underline{d}_6$): δ 0.05 (Me_2Si), 0.85 (4 x Me-thex), 1.15 (Me_3C-piv), 1.6 (C$\underline{H}Me_2$ thex), 3.75 (5'-CH_2), 4.85 (H-4'), 5.7 (H-5), 5.75 (OCH_2N), 6.0 (H-2'), 6.4 (H-3'), 6.8 (H-1'), 7.7 (H-6)

^{13}C NMR (50 MHz, DMSO-$\underline{d}_6$) δ:-3.6 ($SiCH_3$), 18.2, 18.3, 20.0, 20.3 (4x CH_3 thexyl), 24.9(Si$\underline{C}Me_2$), 26.6($\underline{C}H_3$ pivaloyl), 33.6($\underline{C}HMe_2$), quaternary pivaloyl C hidden, 64.4 (C5'), 64.8 (NCH_2), 87.4 (C4'), 90.5 (Cl'), 101.0 (C5), 126.1 (C2'), 135.3 (C3'), 140.9(C6), 150.8 (C2), 161.2 (C4), 177.0 (C=O acyl)

c. <u>3-Pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil</u>. A solution of anhydrous tetrabutylammonium fluoride in dry THF (0.2 g/ml, 13 ml) was added dropwise with stirring to a solution of 3-pivaloyloxymethyl-1-(5-0-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (2.25 g, 4.98 mmol) under nitrogen at 0°C. The solution was stirred at ambient temperature for 35 min, the solvent evaporated, water (10 ml) and chloroform (100 ml) added, the mixture shaken, the chloroform layer evaporated and the residual material subjected to flash chromatography on silica gel using chloroform:diethyl methanol (95:5); yield 1.22 g (76 %) of a colourless glassy solid.

Example 22

3-α-(Ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil

a. 3-α-(Ethyloxycarbonyloxy)ethyl-1-(5-O-thexyldimethylsilyl-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil. Anhydrous potassium carbonate (35 mg, 0.25 mmol) was added to a solution of 1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (80 mg, 0.23 mmol) in DMF (5 ml). The suspension was stirred vigorously under nitrogen at ambient temperature for 2.5 hour, cooled to 0°C and chloroethyl ethyl carbonate (46 mg, 0.300 mmol) in DMF (1 ml) added, the mixture stirred at 40°C for 2 days, the solvent removed at reduced pressure, the residue extracted with hexane:ethyl acetate (7:5) and the filtrate subjected to flash chromatography using the above eluant; yield 69 mg (65 %) of a colourless oil.

^{1}H NMR (200 MHz,DMSO-d_6): δ 0.05 (Me_2Si), 0.85 (4 x Me-thex), 1.2 and 4.1 (OEt), 1.6 (C<u>H</u>Me_2-thex), 1.75 (d, <u>Me</u>CH), 3.75 (5'-CH_2), 4.85 (H-4'), 5.65 (H-5), 5.95 (H-2'), 6.4 (H-3'), 6.8 (H-1'), 7.05 (OCHN), 7.65 (H-6)

^{13}C NMR (50 MHz, DMSO-d_6): δ $SiMe_2$ (not observed), 13.9 (<u>Me</u>CH_2), 17.38/17.48 (<u>Me</u>CH), 18.2, 18.33, 20.00, 20.25 (4x <u>Me</u>-thex), 24.9 (Si<u>C</u>Me_2), 33.6 (<u>C</u>HMe_2), 64.1 and 64.3 (5'-CH_2 and <u>C</u>H_2Me), 76.7/76.8 (N<u>CH</u>MeO), 87.3 (C-4'), 90.2 (C-1'), 101.2 (C-5), 126.25 (C-2'), 135.15 (C-3'), 140.4 (C-6), 150.1 (C-2), 153.6 (<u>C</u>O-ester), 161.5 (C-4). A double set of signals in some cases are seen because the product is a diastereoisomeric mixture.

b. 3-α-(Ethyloxycarbonyloxy)ethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil. A solution of anhydrous tetrabutylammonium fluoride (77 mg, 0.294

mmol) in dry THF (3 ml) was added dropwise with stirring to a solution of 3-α-(ethyloxycarbonyloxy)ethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (69 mg, 0.147 mmol) in dry THF (3 ml) under nitrogen at 0°C and the mixture stirred at ambient temperature for 35 min. The solvent was then evaporated, the residue extracted with chloroform (10 ml), washed and dried ($MgSO_4$), the solution evaporated and the residual material subjected to flash chromatography on silica gel using chloroform:methanol (95:5); yield 21 mg (46 %).

^{1}H NMR (200 MHz, DMSO-$\underline{d}_6$): δ 1.20 and 4.12 (OEt), 1.73 (d, <u>Me</u>CH), 3.59 (5'-CH_2), 4.81 (H-4'), 5.01 (OH), 5.71 (H-5), 5.93 (H-2'), 6.42 (H-3'), 6.85 (H-1'), 7.04 (OCHN), 7.79 (H-6)

^{13}C NMR (50 MHz, DMSO-$\underline{d}_6$) δ:14.0 and 64.2 ($\underline{C}H_3\underline{C}H_2$), 17.5, 17.6 ($\underline{C}H_3CH$), 62.3 (C5'), 76.8, 76.9 (NCO), 87.9 (C4'), 90.2 (C1'), 101.1 (C5), 125.9 (C2'), 135.8 (C3'), 140.9 (C6), 150.3 (C2), 153.6 (<u>C</u>O-ester), 161.7 (C4).

Example 23

1-(5-O-acetyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)3-α-(ethyloxycarbonyloxy)ethyluracil

1-(5-O-Acetyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (100 mg, 0.396 mmol) and potassium carbonate (63 mg, 0.44 mmol) were suspended in DMF (5 ml), the mixture stirred at ambient temperature under nitrogen for 1 hour, cooled to 0°C, 1-chloroethyl ethyl carbonate (0.52 mmol) added, the mixture stirred at 60°C for 44 hours and the solvent evaporated at reduced pressure. The residual product was purified by flash chromatography on silica gel using chloroform:methanol (50:1); yield 77 mg (53 %) of an oily material.

^{1}H NMR (200 MHz,DMSO-$\underline{d}_6$) δ 1.2 and 4.1 (OEt), 1.75 ($\underline{Me}$CH), 2.05 (MeCO), 4.2 (5'-CH_2), 5.05 (H-4'), 5.8 (H-5), 6.05 (H-2'), 6.45 (H-3'), 6.85 (H-1'), 7.05 (OC$\underline{H}$N), 7.5 (H-6)

^{13}C NMR (50 MHz, DMSO-$\underline{d}_6$) δ:13.9 and 64.6 ($\underline{C}H_3\underline{C}H_2$), 17.5, ($\underline{C}H_3$CH), 20.6 ($\underline{C}H_3$ acetyl), 64.1 (c5'), 76.8 (N$\underline{C}$O), 84.2(c4'), 90.4(cl'), 101.5(c5), 126.6(c2'), 134.5(c3'), 140.3(c6), 150.2(c2), 153.6 (CO-ester), 161.6(c4) 170.6 (CO acetyl).

Example 24

1-(5-O-Ethyloxycarbonyloxy-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)3-α-(ethyloxycarbonyloxy)ethyluracil

Sodium hydride (80 % dispersion in oil; 0.5 mmol) was added to a solution of 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (50 mg, 0.238 mmol) in dry DMF (1 ml), the mixture stirred at ambient temperature under nitrogen for 1 hour, cooled to 0°C, 1-chloroethyl ethyl

carbonate (0.52 mmol) added, the mixture stirred at 60°C for 26 hours and the solvent evaporated at reduced pressure. The residue was extracted with diethyl ether, the extracts washed with 1M aqueous ammonium chloride, dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography on silica gel using chloroform:methanol (50:1); yield 18 mg (19 %).

^{1}H NMR (200 MHz,DMSO-$\underline{d}_6$): δ 1.2 and 4.1 (2 x OEt), 1.73 ($\underline{Me}$CH), 4.28 (5'-CH_2), 5.02 (H-4'), 5.68 (H-5), 6.03 (H-2'), 6.47 (H-3'), 6.85 (H-1'), 7.04 (OCHN), 7.46 (H-6)

^{13}C NMR (50 MHz, DMSO-$\underline{d}_6$) δ:13.9, 14.0 (2x$\underline{C}H_3CH_2$), 17.4, 17.5 ($\underline{C}H_3$CH), 63.96, 64.15, (Me$\underline{C}H_2$O and c5'), 67.7 (Me$\underline{C}H_2$O), 76.8 (NCO), 84.1(c4'), 90.4(cl'), 101.3(c5), 126.7(c2'), 134.2(c3'), 140.3(c6), 150.2(c2), 153.6 (CO-ester), 154.6 (CO-ester), 161.5(c4).

Example 25

N^6-Ethyloxycarbonyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine

a. 9-(5-O-Thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine. Thexyldimethylsilyl chloride (1 ml) was added to a mixture of 9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (200 mg) and imidazole (1.0g) in dry pyridine (3 ml) under nitrogen and the mixture stirred at ambient temperature for 2 hours, water (50 ml) added, the mixture extracted with chloroform (2 x 50 ml), the washed and dried chloroform solution evaporated and the residue subjected to flash chromatography on silica gel using chloroform: methanol (10:1); yield 300 mg of a colourless oily material.

b. N^6-Ethyloxycarbonyl-9-(5-0-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine. Ethyl chloroformate (147 mg, 1.6 mmol) was added to a solution of N-methylimidazole (131 mg, 1.6 mmol) in dichloromethane (1 ml) at 0°C, the mixture stirred at this temperature for 30 min before the addition of a solution of 9-(5-0-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (300 mg) in dichloromethane (1 ml). The mixture was stirred at ambient temperature for 14 hours, the solvent removed at reduced pressure, the residue subjected to flash chromatography on silica gel using ethyl acetate; yield 10 mg.

^{1}H NMR (200 MHz, $CDCl_3$) δ:0.05 (Me_2Si), 0.85 (4 x Me-thex), and 4.28 (OEt), 1.6 ($\underline{CH}Me_2$-thex), 3.77 (5'-CH_2), 4.96 (H-4'), 6.02 (H-2'), 6.38 (H-3'), 7.11 (H-1'), 8.19 (H-2), 8.74 (H-8), 9.16 (NH).

^{13}C NMR (50 MHz, $CDCl_3$) δ:-3.4 ($\overset{Me}{\cancel{M-e)}}{}_2$Si), 14.6 and 62.4 ($\underline{C}H_3\underline{C}H_2O$), 18.57, 18.62, 20.5, 20.6 (4x $\underline{C}H_3$ thexyl), 25.7 (ME_2C-thexyl), 34.3 ($CHMe_2$), 65.0 (c5'), 88.3(c4'), 88.8(cl'), 125.7(c2'), 135.5(c3'), 141.9(c8), 150.0, 151.6, 153.6 (c2, c4, c6), C=O not observed.

c. N^6-Ethyloxycarbonyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine. A solution of anhydrous tetrabutylammonium fluoride (48 mg) in dry THF (1 ml) was added dropwise with stirring to a solution of N^6 -ethyloxycarbonyl-9-(5-0-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (10 mg) in THF (1 ml) under nitrogen at 0°C. The solution was stirred at ambient temperature for 30 min, the solvent evaporated, water (20 ml) and chloroform (10 ml) added, the mixture shaken, the chloroform layer evaporated and the residual material subjected to flash chromatography on silica gel using chloroform:diethyl methanol (10:1); yield 3 mg

^{1}H NMR (200 MHz, $CDCl_3$) δ:1.34 and 4.32 (OEt), 3.9-4.0 (5'-CH_2), 4.50 (OH), 5.11 (H-4'), 6.02 (H-2'), 6.51 (H-3'), 6.99 (H-1'), 8.10 (H-2), 8.18 (NH), 8.69 (H-8)

^{13}C NMR (50 MHz, $CDCl_3$) δ:14.6 and 62.6 ($\underline{C}H_3\underline{C}H_2O$), 64.1, (c5'), 89.1(c4'), 90.8(cl'), 115.1(c5), 126.1(c2'), 135.4(c3'), 142.3(c8), 150.3, 151.4, 153.3(c2,c4,c6), C=O not observed.

Example 26

N^6-Ethyloxycarbonyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (alternative synthesis)

a. N^6-Ethyloxycarbonyl-9-(5-0-α-acetoxyisobutyryl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine. N-Methyl imidazole (7 mmol) and ethyl chloroformate (7 mmol) were added to a solution of 9-(5-0-α-acetoxyisobutyryl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (250 mg, 0.69 mmol), the mixture stirred at ambient temperature for 12 hours, the solvent evaporated and the product purified by flash chromatography on silica gel using chloroform:methanol (50:1); yield 135 mg (45 %).

^{1}H NMR (200 MHz, $CDCl_3$) δ:1.34 and 4.3 (OEt), 1.52 ($\underline{Me}_2CH$), 2.02 (MeCO), 4.3 (5'-CH_2), 5.16 (H-4'), 6.14 (H-2'), 6.40 (H-3'), 7.15 (H-1'), 8.22 (H-2), 8.67 (NH), 8.77 (H-8)

^{13}C NMR (50 MHz, $CDCl_3$) δ:14.5 and 62.4 ($\underline{C}H_3\underline{C}H_2O$), 21.3 ($CH_3$ acetyl), 24.6, 24.8 (2x CH_3 isobutyryl), 65.9 (c5'), quatern. isobutyryl C hidden, 85.2(c4'), 89.0(cl'), 122.6(c5), 126.5(c2'), 134.2(c3'), 141.3(c8), 150.2, 151.68, 151.73, 153.7 (c2,c4,c6, CO-ester), 170.7 (C=O acetyl), 173.0 (C=O isobutyryl).

b. <u>N^6-Ethyloxycarbonyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine</u>. Sodium hydride (80% dispersion in oil, 5 mg) was added to a solution of N^6-ethyloxycarbonyl-9-(5-O-α-acetoxyisobutyryl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (20 mg) in dry DMF (0.5 ml) with stirring, the mixture stirred at ambient temperature for 3 min before a stream of dry ammonia was passed through the mixture for 15 min. Water (10 ml) was then added, the mixture freeze-dried and the residue subjected to flash chromatorgraphy on silica gel using chloroform:methanol (10:1); yield 16 mg.

<u>Example 27</u>

<u>N^6-Ethyloxycarbonyl-9-(5-O-pivaloyloxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine and N^6-ethyloxycarbonyl-N^6-pivaloyloxymethyl-9-(5-O-pivaloyloxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine</u>. Sodium hydride (80 % dispersion in oil, 5 mg) was added to a solution of N4-ethyloxycarbonyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (16 mg) in dry DMF (1 ml) with stirring, the stirring continued for 3 min before chloromethyl pivalate (excess) was added and the mixture stirred at ambient temperature overnight. The solvent was then removed at reduced pressure and the residue subjected to flash chromatography on silica gel using chloroform:methanol (50:1). The products were well separated:

<u>N^6-Ethyloxycarbonyl-9-(5-O-pivaloyloxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine</u>

^{1}H NMR (200 MHz,$CDCl_3$) δ:1.15 (3xCH_3 pivaloyl), 1.35 and 4.35 ($C\underline{H}_3C\underline{H}_2O$), 3.85 (5'-$CH_2$), 5.1 (H-4'), 5.15 and 5.25 (OCH_2O), 6.05 (H-2'), 6.4 (H-3'), 7.15 (H-1'), 8.0 (NH),

8.2 (H-2) 8.8 (H-8)

N^6-ethyloxycarbonyl-N^6-pivaloyloxymethyl-9-(5-O-pivaloyloxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine

^1H NMR (200 MHz, $CDCl_3$; signals from lower field region) δ:3.73 (s, H-5'-b), 3.83 (t H5'-a), 4.32 ($CH_3\underline{CH_2}O$), 4.85(H-4'), 5.08 (d, OCHO-b), 5.50 (d, OCHO-a), 6.02 (OCH_2N), 6.05 (H-2') 6.4 (H-3'), 7.19 (H-1')

^{13}C NMR (50 MHz, $CDCl_3$) δ:14.5 and 63.5 ($\underline{C}H_3\underline{C}H_2O$), 27.2 ($\underline{Me_2}C$), 39.1 ($Me_2\underline{C}$), 70.9, 71.9, 86.0, 86.0, 86.2, 88.6, 89.2, 89.5, 126.1(c2'), 134.7(c3'), 143.2(c8), 152.6(c2)

Example 28

1-Pivaloyloxymethyl-9-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)hypoxanthine.

a. 1-Pivaloyloxymethyl-9-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)hypoxanthine

Chloromethyl pivalate (68 mg, 0.30 mmol) was added dropwise through a syringe to a solution of 9-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)hypoxanthine(40 mg, 0.11 mmol) in dry DMF (5 ml) under nitrogen with stirring at 0°C and the mixture stirred at ambient temperature until monitoring by TLC showed that the reaction was complete (35 min). The mixture was evaporated under reduced pressure and the oily residue purified by flash chromatography on silica gel using chloroform:ethanol:diethyl ether (5:4:1); yield 34 mg (67 %).

^1H NMR (200 MHz, $CDCl_3$): δ 0.03 (Me_2Si), 0.85 (Me_3CSi), 1.25 (Me_3C), 3.79 (5'-CH_2), 4.96 (H-4'), 5.98 (OCH_2O),

6.00 (H-2'), 6.49 (H-3'), 6.95 (H-1'), 8.00 (H-8), 8.26 (H-2).

b. 1-Pivaloyloxymethyl-2-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)hypoxanthine

Tetrabutylammonium fluoride in THF (0.25 M; 1.60 ml, 0.40 mmol) was added to a solution of 1-pivaloyloxymethyl-9-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)hypoxanthine (34 mg, 0.073 mmol) in dry THF (3 ml) with stirring under nitrogen at 0°C, the mixture stirred at ambient temperature for 40 min, the solvent removed by evaporation and the residual material subjected to flash chromatography on silica gel using chloroform:ethanol (9:1); yield 20 mg (78 %) of an oily material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (Me_3C), 3.20 (5'-CH_2), 5.10 (OH), 5.20 (H-4'), 6.00 (OCH_2N), 6.19 (H-2'), 6.21 (H-3'), 7.0 (H-1'), 7.98 (H-8), 8.08 (H-2).

Example 29

3'-Fluoro-3-propionyloxymethyl-3'-deoxythymidine

a. Chloromethyl propionate was prepared by the method described by Benneche et al. (Acta Chem. Scand., 43, (1988), 74). Bp. 53°C/3 mm Hg

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.17 (t, 3H, CH_3), 2.43 (q, 2H, $C\underline{H_2}$-CH_3), 5.70 (s, 2H, $ClCH_2O$).

b. 3'-Fluoro-5'-o-trityl-3'deoxythymidine (200 mg, 0.413 mmol, was prepared as described in Example 30) was dissolved in DMF (2 ml), potassium carbonate (62.8 mg, 0.54 mmol) was added and the suspension stirred at ambient temperature for 1 hour. The mixture was cooled

to 0°C, chloromethyl propionate (74 mg,, 0.604 mmol) added and stirred at ambient temperature for 42 hours before the solvent was evaporated and the residue chromatographed on silica gel using ethyl acetate - light petroleum (35:65); yield 173 mg (73%) of 3'-fluoro-3-propionyloxymethyl-5'-O-trityl-3'-deoxythymidine as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, J 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 1.41 (s,3H, 5-CH_3), 2.15-2.80 (m, 4H, $\underline{CH_2}$-CH_3, H-2'), 3.45 (m, 2H, H-5'), 4.33 (d, 1H, H-4'), 5.31 (dd, 1H, H-3'), 5.98 (s, 2H, NCH_2O), 6.5 (m, 1H, H-1'), 7.2-7.45 (m, trityl), 7.63 (d, 1H, H-6)

^{13}C NMR (50 MHz, $CDCl_3$): δ 9.00 ($CH_2\underline{CH_3}$), 12.47 (5-CH_3), 27.43 ($\underline{CH_2}$-CH_3), 39.10 ($J_{2',F}$21.2 Hz, C-2'), 63.86 ($J_{5'-F}$10.8 Hz, C-5') 65.09 (OCH_2N), 84.57 ($J_{4'-F}$25.7 Hz, C-4'), 85.64 (C-1'), 88.21 ($Ph_3\underline{C}$), 94.91 ($J_{3',F}$178.6 Hz, C-3'), 111.39 (C-5), 128.15, 128.66, 129.09, 143.51 (Trityl), 134.82 (C-6), 150.99 (C-2), 163.12 (C-4), 174.03 (COO).

c. 3'-Fluoro-3-propionyloxymethyl-5'-o-trityl-3'-deoxythymidine (mg, mmol) was dissolved in ethanol (5 ml), acetic acid (0.25 ml) added and the mixture refluxed for 8 hours. Water (3 ml) was added and the mixture was evaporated at reduced pressure. The residue was chromatographed on silica gelusing ethyl acetate - light petroleum (5:1); yield 47 mg (64 %) as a glassy material.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 (t, J 7.5 Hz, 3H, CH_2-CH_3), 1.92 (d, 3H, 5-CH_3), 2.2-2.7 (m, 5H, H-2', $\underline{CH_2}$-CH_3), 3.8-4.0 (m, 2H, H-5'), 4.32 (d, 1H, H-4'), 5.3 (m, 1H, H-3'), 5.96 (s, 2H, NCH_2O), 6.2 (m, 1H, H-1'), 7.48 (d, 1H, H-6).

Example 30

3'-Fluoro-3-pivaloyloxymethyl-3'-deoxythymidine

a. 3'-Fluoro-5'-O-trityl-3'-deoxythymidine was prepared as described by Herdewijn et al. (J.Med.Chem.,30, (1987), 1270). The product was isolated by chromatography on silica gel using diethylether to furnish 3'-fluoro-5'-O-trityl-3'-deoxythymidine as a white solid (R_f = 0.39 on pre-coated Merck silica gel F_{254} plates using diethyl ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 3H, 5-CH_3) 2.15-2.85 (m, 2H H-2'), 3.45 (m, 2H, H-5'), 4.33 (d, 1H, H-4'), 5.31 (dd, 1H, H-3'), 6.5 (m, 1H, H-1'), 7.2-7.4 (m, trityl), 7.60 (s, 1H, H-6), 9.50 (bs, 1H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 11.77 (CH_3), 38.78 ($J_{2',F}$ 21.2 Hz, C-2'), 63.63 ($J_{5',F}$ 10.6 Hz, C-5'), 84.17 ($J_{4',F}$ 25.6 Hz, C-4'), 84.78 (C-1'), 87.86 (Ph_3C), 94.34 ($J_{3',F}$ 178.2 Hz, C-3'), 111.59 (C-5), 127.61, 128.12, 128.68 and 143.20 (Ph), 135.14 (C-6), 150.45 (C-2), 163.70 (C-4).

MS(CI-isobutane): 487 [M+H] (6.5%).

b. 3'-Fluoro-5'-O-trityl-3'-deoxythymidine (106 mg, 0.219 mmol) was dissolved in DMF (1 ml), potassium carbonate (34.3 mg, 0.248 mmol) added and the resulting suspension stirred for 1 hour at ambient temperature. Chloromethyl pivalate (42.5 μl, 0.293 mmol) was added and the mixture stirred for 46 hours before the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using hexane-ethyl acetate (70:30); yield 104 mg (79%) of 3'-fluoro-3-pivaloyloxymethyl-5'-O-trityl-3'-deoxythymidine as glassy material which was triturated with light petroleum ether to give a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (s, 9H, t-Bu), 1.42 (s, 3H, 5-CH_3), 2.15-2.8 (m, 2H, H-2'), 3.45 (m, 2H, H-5'), 4.3 (dm, 1H, H-4'), 5.3 (m, 1H, H-3'), 5.94 (s, 2H, CH_2), 6.5 (m, 1H, H-1'), 7.2-7.4 (m, trityl), 7.62 (d, 1H, H-6).

c. 3'-Fluoro-3-pivaloyloxymethyl-5'-O-trityl-3'-deoxythymidine (92 mg, 0.154 mmol) was dissolved in ethanol (3 ml), the solution refluxed and acetic acid (150 μl) added in portions over 1.5 hours. The solution was further refluxed for 6 hours, cooled, evaporated, toluene (1 ml) added and the mixture re-evaporated. Addition of toluene and re-evaporation was repeated once. The residue was chromatographed on silica gel using diethyl ether; yield 31.8 mg (58%) of the title compound which was triturated with light petroleum to give a white solid, mp. 88°C (uncorrected).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 9H, t-Bu), 1.93 (d, 3H, 5-CH_3), 2.25-2.6, (m, 3H, H-2' and OH), 3.75-4.0 (m, 2H, H-5'), 4.33 (d, 1H, H-4'), 5.3 (dm, 1H, H-3'), 5.93 (s, 2H, CH_2), 6.2 (m, 1H, H-1'), 7.44 (d, 1H, H-6).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.37 (5-CH_3), 27.23 ($C(CH_3)_3$), 38.02 ($J_{2',F}$ 20.9 Hz, C-2'), 39.10 ($C(CH_3)_3$), 62.90 ($J_{5',F}$ 10.9 Hz, C-5'), 65.39 (CH_2), 85.66 ($J_{4',F}$ 25 Hz, C-4'), 88.64 (C-1'), 94.80 ($J_{3',F}$ 177.6 Hz, C-3'), 111.15 (C-5), 136.45 (C-6), 150.99 (C-2), 162.98 (C-4), 178.22 (COO).

MS(CI-NH_3): 376[M+NH_4] (8.4%), 359 [M+H] (100%).

<u>Example 31</u>

<u>3-α-(Ethyloxycarbonyloxy)ethyl-3'-fluoro-3'-deoxythymidine</u>

a. 3'-Fluoro-5'-O-trityl-3'-deoxythymidine (200.7 mg, 0.414 mmol, prepared as described Example 30 was

dissolved in DMF (3 ml), potassium carbonate (63.4 mg, 0.459 mmol) added and the suspension stirred for 1 hour at ambient temperature before 1-chloroethyl ethyl carbonate (72 μl, 0.537 mmol) was added. The mixture was stirred at 50°C for 15 hours when TLC showed partial conversion of the starting material. Additional 1-chloroethyl ethyl carbonate (56 μl, 0.418 mmol) was therefore added and the mixture stirred for another 25 hours, cooled, the solvent evaporated under reduced pressure and the residue chromatographed on silica using light petroleum - ethyl acetate (7:3); yield 158.7 mg (64%) of 3-α-(ethyloxycarbonyloxy)ethyl-3'-fluoro-5'-O-trityl-3'-deoxythymidine as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J7 Hz, 3H, CH_2-$C\underline{H}_3$), 1.40 (s, 3H, 5-CH_3), 1.85 (d, J 6.5 Hz, 3H, CH-$C\underline{H}_3$), 2.1-2.85 (m, 2H, H-2'), 3.45 (m, 2H, H-5'), 4.1-4.45 (m, 3H, H-4', OCH_2), 5.29 (dd, 1H, H-3'), 6.5 (m, 1H, H-1'), 7.2-7.4 (m, trityl), 7.54 (s, 1H, H-6).

b. The 3-α-(ethyloxycarbonyloxy)ethyl-3'-fluoro-5'-O-trityl-3'-deoxythymidine (116 mg, 0.194 mmol) was dissolved in ethanol (5 ml), acetic acid (0.250 ml) added and the mixture refluxed for 7 hours, the solvent removed at reduced pressue, toluene (2 ml) added and the mixture was re-evaporated. The addition of toluene and re-evaporation was repeated once. The residue was chromatographed on silica using diethyl ether; yield 35 mg (51%) of the title compound as an oil which was triturated with diethyl ether and light petroleum to give a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, CH_2-$C\underline{H}_3$), 1.82 (d, 3H, CH-$C\underline{H}_3$), 1.87 (d, 3H, 5-CH_3), 2.15-2.75 (m, 3H, OH, H-2'), 3.75-3.95 (m, 2H, H-5'), 4.05-4.35 (m, 3H, H-4', CH_3-$C\underline{H}_2$-O), 5.28 (m, 1H, H-3'), 6.24 (m, 1H, H-1'), 7.20 (m, 1H, $C\underline{H}$-CH_3), 7.45 (s, 1H, H-6).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.42, 14.31 (5-CH_3, CH_2-$\underline{C}H_3$), 18.06 (CH-$\underline{C}H_3$), 38.22 ($J_{2',F}$ 20.6 Hz, C-2'), 62.79 ($J_{5',F}$ 10.9 Hz, C-5'), 64.77 (OCH_2), 77.84 ($\underline{C}$H-CH_3), 85.56 ($J_{4',F}$ 24.7 Hz, C-4'), 87.72 (C-1'), 94.85 ($J_{3',F}$ 177.8 Hz, C-3'), 111.14 (C-5), 135.96 (C-6), 150.49 (C-2), 154.41 (OCOO), 163.15 (C-4).

Example 32

5'-O-Acetyl-5-chloro-3'-fluoro-3-pivaloyloxymethyl-2',3'-deoxyuridine

a. 5'-O-Acetyl-5-chloro-3'-fluoro-2',3'-deoxyuridine was prepared as described by Van Aerschot et al. (J.Med.Chem. 32 (1989), 1743). The product was purified by chromatography on silica gel using ethyl acetate-light petroleum (6:4).

^1H NMR (200 MHz, $CDCl_3$): δ 1.9-2.9 (m, 5H, CH_3, H-2'), 4.2-4.6 (m, 3H, H-4', H-5'), 5.19 (dd, 1H, H-3'), 6.3 (m, 1H, H-1'), 7.75 (s, 1H, H-6), 9.1 (bs, 1H, NH).

b. 5'-O-Acetyl-5-chloro-3'-fluoro-2',3'-deoxyuridine (79 mg, 0.258 mmol) was dissolved in DMF (2 ml), potassium carbonate (39 mg, 0.282 mmol) was added and the resulting suspension stirred at ambient temperature for 1 hour. Chloromethyl pivalate (49 μl, 0.337 mmol) was added and the mixture stirred for 24 hours before the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate-light petroleum (45:55); yield 85 mg (78%) of the title compound as an oil.

^1H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 9H, t-Bu), 1.9-2.9 (m, 5H, CH_3, H-2'), 4.2-4.6 (m, 3H, H-4', H-5'), 5.19 (dd, 1H, H-3'), 5.94 (s, 2H, CH_2), 6.35 (m, 1H, H-1'), 7.78 (s, 1H, H-6).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.96 (CH_3), 27.17 ($C(\underline{C}H_3)_3$), 39.07 ($\underline{C}(CH_3)$), 39.24 (C-2'), 63.83 ($J_{2',F}$ 10.7 Hz, C-5'), 65.83 (CH_2), 83.32 ($J_{4',F}$ 26.6 Hz, C-4'), 86.90 (C-1'), 93.75 ($J_{3',F}$ 180.7 Hz, C-3'), 109.48 (C-5), 135.64 (C-6), 149.63 (C-2), 158.45 (C-4), 170.55 ($CH_3\underline{C}O$), 177.96 (t-Bu$\underline{C}$O).

Example 33

1-(5-O-Hemisuccinyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethylthymine

a. 1-(5-O-Hemisuccinyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine

1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.205 g, 0.915 mmol) and succinic anhydride (0.170 g, 0.915 mmol) were dissolved in pyridine (10 ml), the solution stirred at ambient temperature for 20 hours before the pyridine was removed at reduced pressure. The product was purified by chromatography on the "chromatotron" using chloroform:ethanol (9:1); yield 0.140 g (65 %) of a white solid.

^1H NMR (300 MHz, DMSO-$\underline{d}_6$): δ 1.78 (5-Me), 2.45 (CH_2CH_2), 4.23 (5'-CH_2), 4.97 (H-4'), 6.00 (H-2'), 6.38 (H-3'), 6.81 (H-1'), 7.29 (H-6), 11.29 (NH).

b. 1-(5-O-Hemisuccinyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethylthymine.

Potassium carbonate (0.129 g, 0.933 mmol) was added to a solution of 1-(5-O-Hemisuccinyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (0.110 g, 0.340 mmol) in DMF (10 ml) under nitrogen, the mixture stirred at ambient temperature for 45 min, cooled to 0°C and chloromethyl pivalate (0.06 ml, 0.419 mmol) added, the mixture stirred at ambient temperature for 12 hours, the solvent

removed at reduced pressure, the residue extracted with chloroform, the mixture filtered, the filtrate evaporated and the product isolated by chromatography on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1), yield 0.076 g (51 %) of a semisolid colourless product.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (Me_3C), 1.83 (5-Me), 2.60 (CH_2CH_2), 4.28 (5'-CH_2), 4.96 (H-4'), 5.74 (OCH_2N), 5.82 (H-2'), 6.21 (H-3'), 7.18 (H-6).

Example 34

N^4-Ethyloxycarbonyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine

a. N^4-Ethyloxycarbonylcytidine

A mixture of cytidine (15.40 g, 63.4 mmol) and diethyl pyrocarbonate (10 ml, 69.1 mmol) in methanol (250 ml) was heated under reflux. Every hour for 4 hours additional diethyl pyrocarbonate (in all 4 x 10 ml) was added and the heating continued for 14 hours. The product crystallized out from the solution on cooling, was filtered off and washed with cold diethyl ether; yield 15.18 g (76 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.23 and 4.16 (OEt), 3.9-4.0 (5'-CH_2, H-2',3',4'), 4.8-5.6 (3 x OH), 5.8 (H-1'), 7.02 (H-5), 8.40 (H-6), 10.33 (NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 14.15, 59.87, 61.19, 68.61, 74.36, 84.10, 89.97, 94.08, 144.64, 153.17, 154.36, 162.71.

b. N^4-Ethyloxycarbonyl-5'-O-thexyldimethylsilylcytidine

Thexyldimethylsilyl chloride (7.00 ml, 35.69 mmol) was

added to a solution of N^4-ethyloxycarbonylcytidine (9.39 g, 29.80 mmol) and imidazole (4.45 g, 65.35 mmol) in DMF (120 ml) under nitrogen at ambient temperature, the mixture stirred at ambient temperature for 26 hours before the solvent was removed by distillation at reduced pressure. The residue was dissolved in a mixture of chloroform:diethyl ether:ethanol (5:4:1; 50 ml) and subjected to flash chromatography on silica gel; yield 10.89 g (80 %).

^{1}H NMR (300 MHz, DMSO-$\underline{d}_6$): δ 0.09 (Me_2Si), 0.86 (tBuSi), 1.22 and 4.15 (OEt), 1.63 (CH-thex), 3.9-4.0 (5'-CH_2, H-2',3',4',5'), 5.5 and 5.6 (2 x OH), 5.76 (H-1'), 7.04 (H-5), 8.26 (H-6), 10.63 (NH).

^{13}C NMR (75 MHz, DMSO-$\underline{d}_6$): δ -3.61, 14.14, 18.13, 18.24, 19.96, 20.12, 24.80, 33.49, 61.20, 61.46, 68.22, 74.50, 83.25, 89.97, 93.03, 143.99, 153.19, 154.19, 162.71.

c. <u>N^4-Ethyloxycarbonyl-2',3'-bis-O((methylthio) thiocarbonyl)-5'-O-thexyldimethylsilycytidine</u>

Sodium hydride (0.300 g, 10.00 mmol in oil) was added gradually to a solution of N^4-ethyloxycarbonyl-5'-O-thexyldimethylsilylcytidine (1.076 g, 2.35 mmol) and imidazole (0.045 g, 0.664 mmol) in dry THF (10 ml) under nitrogen at 0°C, the mixture stirred at 0°C for 1 hour, carbon disulfide (0.800 ml, 13.24 mmol) added, the stirring continued for 30 min, methyl iodide (0.600 ml, 9.60 mmol) added and the stirring was continued for another 30 min. The reaction was worked up by the addition of diethyl ether (50 ml), the solution washed with water (2 x 5 ml), dried ($MgSO_4$) and the solvents distilled off. The residual material was subjected to flash chromatography on silica gel using chloroform:ethyl acetate (9:1) and thereafter chromatography on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.51 g

chloroform:diethyl ether:ethanol (5:4:1); yield 0.51 g (34 %).

^{1}H NMR (300 MHz, DMSO-$\underline{d}_6$): δ 0.09 (Me_2Si), 0.86 (4 x Me-thex), 1.21 and 4.16 (OEt), 1.60 (CH-thex), 2.57 and 2.61 (2 x SMe), 3.92 (5'-CH_2), 4.52 and 6.1-6.3 (4 x CH), 7.09 (H-5), 8.14 (H-6) and 10.80 (NH).

^{13}C NMR (75 MHz, DMSO-$\underline{d}_6$): δ -3.61, -3.64, 14.12, 18.22, 18.27, 18.62, 18.71, 19.95, 20.08, 24.70, 33.46, 61.37, 62.43, 78.34, 80.21, 82.46, 89.16, 94.92, 145.21, 153.04, 153.86, 163.42, 214.13, 214.38.

d. <u>N^4-Ethyloxycarbonyl-1-(5'-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine</u>

A solution of N^4-ethyloxycarbonyl-2',3'-bis-O-((methylthio)thiocarbonyl)-5'O-thexyldimethylsilylcytidine (0.476 g, 0.747 mmol) and azobisisobutyronitrile (0.070 g, 0.427 mmol) in toluene (50 ml) was heated to reflux and tributylstannane (1.30 ml, 4.919 mmol) added. The mixture was heated under reflux for 20 min before the solvent was distilled off. The product was isolated from the residual material by chromatorgraphy on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.228 g (72 %) of a white solid.

^{1}H NMR (300 MHz, DMSO-$\underline{d}_6$): δ 0.09 (Me_2Si), 0.86 (4 x Me-thex), 1.21 and 4.16 (OEt), 3.80 (5'-CH_2), 5.18 (H-4'), 6.00 (H-2'), 6.36 (H-3'), 6.86 (H-1'), 7.02 (H-5), 8.14 (H-6), 10.63 (NH).

e. <u>N^4-Ethyloxycarbonyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine</u>

Anhydrous tetrabutylammonium fluoride in THF (0.25 M, 2 ml) was added dropwise over 10 min with stirring to a

solution of N^4-ethyloxycarbonyl-1-(5'-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine (0.209 g, 0.494 mmol) in dry THF (5 ml) under nitrogen at 0°C, the mixture stirred at ambient temperature for 1 hour, more tetrabutylammonium chloride solution (2 ml) added and the mixture stirred for 1 hour. The reaction was stopped by the addition of an aqueous saturated solution of ammonium chloride (2 ml), the mixture was stirred for 10 min, the solvents removed at reduced pressure, the residue extracted with chloroform and the mixture filtered, the filtrate evaporated and the residue chromatographed on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1); yield 0.054 g (39 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 and 4.24 (OEt), 3.7-4.0 (5'-CH_2), 5.02 (H-4'), 6.02 (H-2'), 6.27 (H-3'), 7.01 (H-1'), 7.20 (H-5), 7.64 (NH), 8.18 (H-6).

Example 35

N^4-Ethyloxycarbonyl-N^4-pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine and N^4-ethyloxycarbonyl-3-pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine

Sodium hydride (0.006 g, 0.200 mmol suspended in oil) was added to a solution of N^4-Ethyloxycarbonyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine (0.047 g, 0.167 mmol) in DMF (5 ml) under nitrogen at 0°C, stirred for 1 hour, cooled to -50°C and chloromethyl pivalate (0.030 ml, 0.209 mmol) added. The mixture was stirred overnight, aqueous saturated ammonium chloride solution (2 ml) added, the mixture stirred for 10 min, the solvents removed under reduced pressure, the residue extracted with chloroform, the mixtured filtered, the filtrate evaporated and the

products separated by chromatography on the "chromatotron" using chloroform:diethyl ether:ethanol (5:4:1).

N^4-Ethyloxycarbonyl-3-pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine was the first product eluted; yield 0.009 g (13 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (Me_3C), 1.26 and 4.14 (OEt), 3.80 (5'-CH_2), 4.87 (H-4'), 5.80 (H-2'), 6.02 (OCH_2N), 6.2-6.3 (H-3',5'), 6.96 (H-1'), 7.45 (H-6).

N^4-Ethyloxycarbonyl-N^4-pivaloyloxymethyl-1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)cytosine was the second product eluted; yield 0.009 g, (13 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (Me_3C), 1.26 and 4.24 (OEt), 3.83 (5'-CH_2), 4.95 (H-4'), 6.0-6.1 (OCH_2N and H-4'), 6.20 (H-3'), 6.98 (H-1'), 7.13 (H-5), 8.04 (H-6).

Example 36

1-(5-Acetoxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethyl-uracil

a. 1-(5-O-Methylthiomethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethyyluracil. A solution of anhydrous tetrabutylammonium fluoride (2.3 ml, 1.8 mmol) in THF was added to a mixture of 3-pivaloyloxymethyl-1-(5-O-thexyldimethylsilyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)uracil (426 mg, 0.91 mmol) and chloromethyl methyl sulfide (0.25 ml, 3.0 mmol) under nitrogen at 0°C, the mixture stirred at 0°C for 3 hours, at ambient temperature for 1 hour before dichloromethane and water was added. The organic phase was separated, dried ($MgSO_4$) and evaporated. The residual material was a mixture of the desired product and 1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-

pivaloyloxymethyluracil which were separated by chromatography on silica gel. The desired product was eluted using hexane:ethyl acetate (1:1).

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.20 (Me_3C), 2.11 (SMe), 3.7-3.9 (5'-CH_2), 4.7 (SCH_2O), 4.9-5.1 (1H, m), 5.77 (H-5), 5.9-6.1 (1H, m), 6.00 (OCH_2N), 6.3-6.5 (1H, m), 7.0-7.2 (1H, m), 7.82 (H-6).

b. <u>1-(5-Acetoxymethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethyl-uracil</u>

Sulfuryl chloride (3.4 mg, 0.025 mmol) in deuteriochloroform (0.2 ml) was added to a solution of 1-(5-O-methylthiomethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethyluracil (11 mg, 0.025 mmol) and cyclohexene (4.1 mg, 0.05 mmol) in deuteriochloroform (1 ml).

<u>1-(5-O-chloromethyl-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)-3-pivaloyloxymethyl-uracil</u> was formed in this reaction. Its formation was monitored by ^{1}H NMR. The reaction had gone to completion after 30 min. The solvent was then removed by evaporation, the residue dissolved in dry DMF (0.1 ml) and added to a suspension of sodium acetate (8 mg, 0.10 mmol) in dry DMF (0.2 ml). The mixture was stirred at ambient temperature for 1 hour before the solvent was evaporated at reduced pressure and dichloromethane and water added to the residue. The organic phase was separated, washed well with brine (x 2), dried ($MgSO_4$), evaporated and the product purified by chromatography on silica gel using hexane:ethyl acetate (1:1); yield 3 mg (31 5).

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.20 (Me_3C), 2.08 (MeCO), 3.8-4.0 (5'-CH_2), 4.9-5.1 (1H, m), 5.28 (OCH_2O), 5.72 (H-5), 6.00 (OCH_2N), 6.3-6.5 (1H, m), 7.2 (1H, m), 7.82 (H-6).

Example 37

3'-Fluoro-5'-O-ethyloxycarbonyl-2'3'-dideoxyuridine

3'-Fluoro-2'3'-dideoxyuridine (50.5 mg, 0.219 mmol, prepared as described by Herdewijn et al. (Nucleosides & Nucleotides, 8, (1989), 65) was dissolved in pyridine (2 ml), 4-dimethylaminopyridine (30 mg, 0.246 mmol) added and the solution cooled to 0°C. Diethyl pyrocarbonate (0.150 ml, 1.04 mmol) was added and the mixture stirred at ambient temperature for 12 hours, the solvent evaporated under reduced pressure, toluene added and the mixture reevaporated. Addition of toluene and reevaporation was repeated once and the residue chromatographed on silica gel using chloroform - methanol (95:5); yield 62 mg (94 %) of title compound as a foam.

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.30 (t, 3H, CH_3) 1.7-2.9 (m, 2H, H-2'), 4.0-5.9 (m, 7H, $\underline{CH_2}$-CH_3, H-5', H-4', H-3', H-5), 6.4 (m, 1H, H-1'), 7.55 (d, 1H, H-6), 8.5 (bs, 1H, NH).

Example 38

3'-Fluoro-5'-O-ethyloxycarbonyl-3-propionyloxymethyl-2',3'-dideoxyuridine

3'-Fluoro-5'-O-ethyloxycarbonyl-2',3-dideoxyuridine (60 mg, 0.198 mmol) and potassium carbonate (34 mg, 0.246 mmol) in DMF (1 ml) was stirred at ambient temperature for 30 minutes before chloromethyl propionate (52 mg, 0.424 mmol) was added. The mixture was stirred at 50°C for 3 hours and partitioned between saturated ammonium chloride (5 ml) and diethyl ether (5 ml). The organic phase was washed with water (3 x 3 ml), dried ($MgSO_4$) and evaporated; yield 55 mg (72 %) of the title compound as an oil. The product can be further purified by

chromatography on silica gel using ethyl acetate-light petroleum (3:2).

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.0-1.5 (m, $\underline{CH_3}$-CH_2-CO,$\underline{CH_3}CH_2$-O) 1.7-2.9 (m, H-2', CH_2-CO), 4.0-5.9 (m, CH_3-$\underline{CH_2}$-O, H-5', H-4', H-3', H-5), 5.95 (s, OCH_2N), 6.4 (m, H-1'), 7.55 (d, H-6).

Pharmaceutical Example A

Preparation of capsules for oral use

Active Compound	50 mg
Amylum maydis	q.s.

The powder is mixed and filled into hard gelatin capsules (Capsugel Size 00).

Pharamceutical Example B

Preparation of an ointment

Active compound	1 g
Liquid paraffin	100 g
White soft paraffin	to 1000 g

White soft paraffin is melted and incorporated into the liquid paraffin and stirred until the mixture is cold. Active compound is triturated with a portion of the basis and gradually the remainder of the basis was incorporated. The ointment is filled into lacquered aluminium tubes (20 g) and sealed. The ointment contains 0.1 % active compound.

Pharmaceutical Example C

Suspension for parenteral administration

Active Compound	200 gram
Polysorbate 80	3 gram
Sorbitol	400 gram
Benzyl alcohol	8 gram
Water	ad 1000 ml
1M HCl	q.s.

Polysorbate 80, Sorbitol and benzyl alcohol are dissolved in 500 ml distilled water. Active compound is screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The pH is adjusted to 4.5 by dropwise addition of 1M HCl. Water is added to 1000 ml, the suspension was filled in 1 ml vials The vials are sterilized by γ-radiation. Each vial contains 200 mg active compound.

Pharmaceutical Example D

Preparation of tablets

	Gram
Active Compound	200
Lactose	85
Polyvinylpyrrolidone	5
Starch	42
Talcum powder	15
Magnesium stearate	3

Active compound and lactose are screened through a 0.15 mm sieve and mixed together for 10 minutes. The mixed powder is wetted with an aqueous solution of polyvinyl-pyrrolidone. The mass is granulated, and the dried (40 °C) granulate is mixed with starch, talcum powder and magnesium stearate. The granulate is compressed into tablets. The tablet diameter is 11 mm, the tablet weight is 350 mg and each tablet contains 200 mg active compound.

Pharmaceutical Example E

Preparation of a suspension for rectal administration

Methyl p-hydroxybenzoate (70 mg) and propyl p-hydroxybenzoate (15 mg) are dissolved in water (100 ml) at 90 °C. After cooling to 30 °C methyl cellulose (2g) is added and the mixture is agitated for 3 hours. 1 gram active compound are screened through a 0.15 mm sieve, and dispersed in the solution under vigorous stirring. The suspension is filled in a 100 ml tube. The suspension contain 10 mg active compound/ml.

Pharmaceutical Example F

Preparation of oral suspension

	Gram
Active Compound	10
Carboxymethyl cellulose	1.5
Sorbitol	200
Sodium benzoate	1.0
Orange essence	0.3
Apricot essence	0.7
Ethanol	50
Water	236.5

Carboxymethyl cellulose, sorbitol and sodium benzoate are dissolved in water with stirring for 2 hours. A solution of the essences in ethanol is added. Active compound is screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The suspension (10 gram) is filled in a 20 ml tube. Each tube contains 200 mg active compound.

Pharmaceutical Example G

Preparation of injection solution

10 mg active compound are dissolved in 10 ml 0.9 % sodium chloride. pH is adjusted to 4.5 with 1N HCl. The

solution is sterile filtered and filled into a 10 ml vial. The solution contains 1 mg active compound/ml.

Pharmaceutical Example H

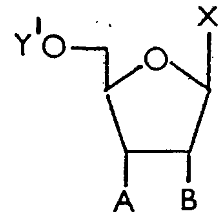
Preparation of tablets (controlled release formulation)

	Gram
Active Compound	500
Hydroxypropylmethylcellulose (Methocel K15)	120
Lactose	45
Povidone	30
Magnesium stearate	5

Active compound hydroxypropyl-methylcellulose and lactose are mixed together for 20 minutes and granulated with a solution of povidone. Magnesium stearate is added and the mixture is compressed into tablets. The tablet diameter is 13 mm, the tablet weight is 700 mg and each tablet contains 500 mg active compound.

CLAIMS

1. Compounds of formula (I)



(I)

(wherein A is a fluorine atom and B is a hydrogen atom or A and B together represents a carbon-carbon bond

Y^1 is a hydrogen atom or a physiologically acceptable group of the formula

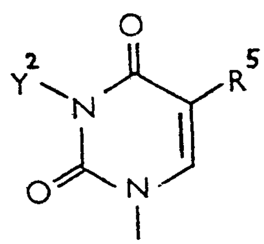
$R^1(O)_nCO(OCR^2R^3)_m-$

where n is 0 or 1, m is 0 or 1 and

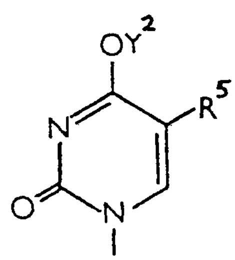
R^1 is an optionally substituted alkyl or aryl group or an N-(C_{1-7} alkyl)-1,4-dihydropyridin- 3-yl group or, where n is 0, a hydrogen atom;

R^2 and R^3 are independently hydrogen atoms or lower alkyl groups; and

X is a group selected from



(A)



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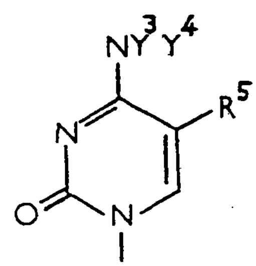

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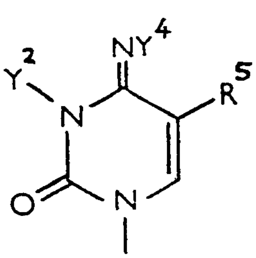

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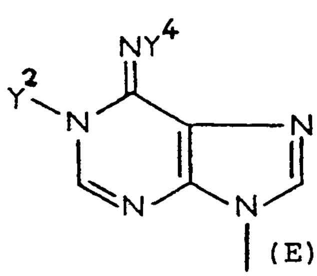
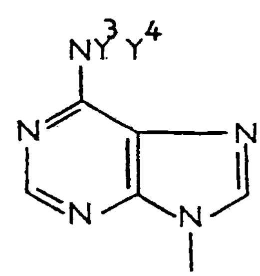
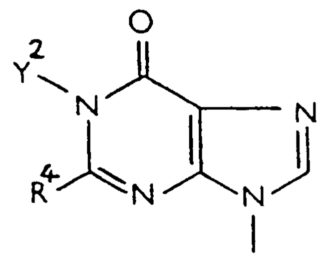
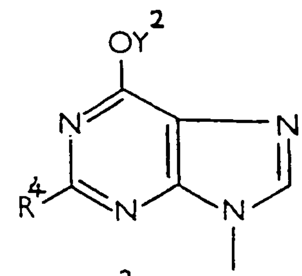


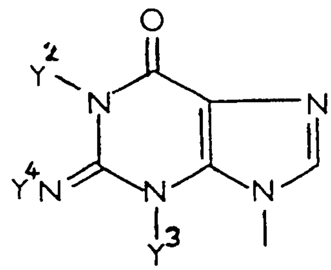
(E)

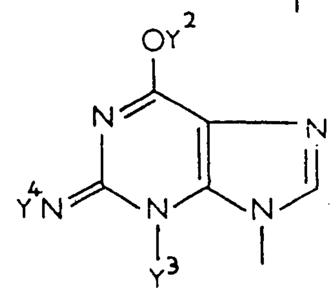


(F)


(G)


(H)


(I)


(J)

(where the groups Y^2, Y^3 and Y^4 are as defined for Y^1 and may be the same as or different from Y^1 or each other, R^4 is a hydrogen atom or a group $-NY^3Y^4$, where Y^3 and Y^4 have the above meanings and R^5 is a hydrogen or halogen atom or a lower alkyl or trifluoromethyl group, with the proviso that at least one of the groups Y^1, Y^2, Y^3 and Y^4 is other than hydrogen, and that when all of those groups Y^2, Y^3 and Y^4 which are present are hydrogen, then Y^1 is a group $R^1(O)_nCO(OCR^2R^3)_m$ in which n and/or m is 1) and/or salts thereof.

2. Compounds of formula (I) as claimed in claim 1 wherein R^1 is selected from optionally substituted C_{1-20} alkyl groups and C_{6-20} aryl groups.

3. Compounds of formula (I) as claimed in claim 1 wherein m represents 1 in at least one of the groups Y^1, Y^2, Y^3 and Y^4; R^2 is a hydrogen atom; and R^3 is a hydrogen atom or a methyl group.

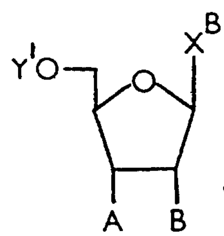
4. Compounds of formula (I) as claimed in claim 1 wherein A and B represent respectively a fluorine atom

and a hydrogen atom.

5. Compounds of formula (I) as claimed in claim 1 wherein A and B represent a carbon-carbon bond.

6. A pharmaceutical composition comprising as active ingredient one or more compounds of formula (I) as defined in any preceding claim and/or a non-toxic salt thereof, together with a pharmaceutical carrier or excipient.

7. A process for the preparation of a compound of formula (I) as defined in any of claims 1 to 5, which comprises reaction of a compound of formula (II)



(II)

[wherein A, B and Y^1 are as defined in claim 1 and X^B is as defined in claim 1 for X except that any of the groups Y^1, Y^2, Y^3 and Y^4 may each additionally represent a protecting group, with the proviso that at least one of Y^1, Y^2, Y^3 and Y^4 is a hydrogen atom] with a reagent serving to introduce a group $R^1(O)_nCO.(OCR^2R^3)_m$ as defined in claim 1 followed where required by removal of any protecting groups and/or unwanted substituents so introduced.

8. Use of compounds of formula (I) as defined in any of claims 1 to 5, and/or salts thereof, in the manufacture of a medicament for the treatment of prophylaxis of retrovirus infections.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01853

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 H 19/06, 19/067, 19/073, 19/16, 19/167, 19/173
A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 H; A 61 K; C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P	EP, A1, 0366171 (NYCOMED AS) 2 May 1990, see the whole document --	1-8
P	EP, A1, 0362967 (NYCOMED AS) 11 April 1990, see the whole document --	1-8
P	EP, A2, 0355031 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 21 February 1990, see the whole document --	1-8
X	EP, A2, 0311100 (F.HOFFMANN-LA ROCHE & CO. AG) 12 April 1989, see part. table 1 and the claims --	1-8

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22nd January 1991	12. 02. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Alfredo Prein

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A1, 0294113 (THE WELLCOME FOUNDATION LIMITED) 7 December 1988, see part. the examples and the claims --	1-8
X	EP, A2, 0254268 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 27 January 1988, see part. pages 3-4 and the claims --	1-8
X	US, A, 3817982 (JULIAN P.H. VERHEYDEN ET AL.) 18 June 1974, see part. col. 1-8, the examples and the claims --	1-8
X	GB, A, 1111989 (MERCK & CO INC.) 1 May 1968, see the whole document --	1-8
A	EP, A2, 0329348 (ELI LILLY AND COMPANY) 23 August 1989, see part. pages 3-5 and the claims --	1-8
A	EP, A1, 0322384 (MEDIVIR AKTIEBOLAG C/O STATENS BAKTERIOLOGISKA LABORATORIUM) 28 June 1989, see part. pages 4-9 --	1-8
A	EP, A2, 0317128 (THE WELLCOME FOUNDATION LIMITED) 24 May 1989, see the claims --	1-8
A	EP, A2, 0292023 (F.HOFFMANN-LA ROCHE & CO. AG) 23 November 1988, see the whole document --	1-8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A2, 0286825 (MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN E.V.) 19 October 1988, see the claims	1-8
A	WO, A1, 8807532 (NYCOMED A.S.) 6 October 1988, see the whole document	1-8
A	J. Med. Chem., Vol. 31, 1988, Piet Herdewijn et al.: "Synthesis and Anti-HIV Activity of Different Sugar-Modified Pyrimidine and Purine Nucleosides ", see page 2040 - page 2048	1-8
A	Biochemical Pharmacology, Vol. 37, No. 14, 1988, Jan Balzarini et al.: "Anti-retrovirus activity of 3'-fluoro- and 3'-azido-substituted pyrimidine 2',3'-dideoxynucleoside analogues ", see page 2847 - page 2856	1-8
A	J. Org. Chem., Vol. 54, 1989, Muzammil M. Mansuri et al.: "Preparation of 1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T) and 2',3'-Dideoxyadenosine (ddA): General Methods for the Synthesis of 2',3'-Olefinic and 2',3'-Dideoxy Nucleoside Analogues Active against HIV", see page 4780 - page 4785	1-8

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 90/01853

SA 41260

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/12/90
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		JP-A-	63303992	12/12/88
		ZA-A-	8803447	22/11/88
EP-A2- 0286825	19/10/88	AU-D-	1308188	22/09/88
		DE-A-	3708849	29/09/88
		EP-A-	0332626	20/09/89
		JP-T-	2500364	08/02/90
		US-A-	4880782	14/11/89
		WO-A-	88/03804	02/06/88
WO-A1- 8807532	06/10/88	AU-D-	1489388	02/11/88
		EP-A-	0342203	23/11/89

For more details about this annex : see Official Journal of the European patent Office, No. 12/82